SOME APPLICATIONS OF BENZOTRIAZOLE AS A SYNTHETIC AUXILIARY

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA
IN PARTIAL FULFILLMENENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1988

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Dedicated to my Family

ACKNOWLEDGMENTS

I would like to express my gratitude to Professor Alan R. Katritzky for guidance, trust, and help during the past three years in his research group.

My special thanks to Professor Bill M. Jones for his encouragment during the very difficult beginning. I would like to thank other members of my committee, Professors Merle A. Battiste, James M. Boncella, and Christopher D. Batich, for their suggestions and discussions.

To Dina, my best friend during these years - caring and helpful - I would like to give my deepest thanks. I want to thank members of the research group Jose, Bogumil, Wang, Yannis, Ping, and Ichiro thanks for all the valuable discussion, support, and their friendship. I am indebted to my colleagues Sutha, Rhonda, Paul, Franz, Jamshed, Craig, and Ramiah for reading this manuscript and polishing my English, and to Steve for introducing me to the darkness of word processing.

Special words go to Marcela, an Argentinian happy soul, my two-year roommate and friend - so far now and yet so close.

Chciałabym podziękować moim przyjaciołom i rodzinie w Polsce, Mamie, Cioci Jadzi, Bratu, Bratowej, Łukaszkowi i Michałkowi za ich pomoc i wiarę we mnie.

I am indebted to all my friends in Italy for helping me survive far from home during the time of martial law. Special thanks go to Professor C. B. Storm and his family for sheltering me and making possible my stay in America.

Lastly to my husband Jim, who read the manuscript and was able to polish and un-Polish my English, for all his struggling with the computer, and the most of all, for being there last year.

TABLE OF CONTENTS

ACKNOWLEDGMENTS - iii

ABSTRACT - vii

CHAPTERS

I GENERAL INTRODUCTION - 1

1.1 General View on the Physical and Chemical Properties of Benzotriazole and Its Applications - - - - - - - - - - - - - - - - - - - 1
1.2 Benzotriazole as a Synthetic Auxiliary - - - - - - - - - - - - - - - - - - 4
1.3 The Phenomena of 1- and 2-Substituted Benzotriazoles - - - - - - - - - 6

II N-MONOALKYLATION OF PRIMARY AMIDES USING BENZOTRIAZOLE - 9

2.1 Introduction - 9
2.1.1 General Methods for Preparation of N-Alkylated Amides - - - - 9
2.1.2 Aim of the Work - 11
2.2 Results and Discussion - 13
2.2.1 Formation of Adducts (**2.3.1**) and (**2.3.2**) - - - - - - - - - - - - 13
2.2.2 Reaction of Adducts (**2.3.1**) and (**2.3.2**) with Sodium Borohydride - 17
2.2.3 Reaction of Adducts (**2.3.1**) and (**2.3.2**) with Lithium Aluminum Hydride - - - - - - - - - - - - - - - - - - - 20
2.2.4 Reactions of the Adducts (**2.3**) with Grignard and Organolithium Reagents - - - - - - - - - - - - - - - - - - - 21
2.3 Conclusions - 25
2.4 Experimental - 26
2.4.1 General Procedure for Preparation of N-[1-(Benzotriazol-1-yl)alkyl]amides (**2.3**) - - - - - - - - - - - - - 26
2.4.2 General Procedure for Preparation of N-Alkylated Amides (**2.6**) - 30
2.4.3 General Procedure for Preparation of N-Alkylated Amines (**2.7**) - 32
2.4.4 General Method for Preparation of Secondary Amides by Reaction of Adducts (**2.3.1**) or (**2.3.2**) with Organometallic Compounds - - - - - - - - - - - - - - - - - - 34

III N-MONOALKYLATION OF PRIMARY THIOAMIDES USING BENZOTRIAZOLE - 38

3.1 Introduction - 38
3.1.1 The Importance and Applications of Thioamides - - - - - - - - - 38
3.1.2 Review of the Methods Available in the Literature for Preparation of N-Alkylated Thioamides - - - - - - - - - - - - 40
3.1.3 Aim of the Work - 43
3.2 Results and Disscussion - 45
3.2.1 Formation of Adducts (**3.10**-**3.12**) - - - - - - - - - - - - - - - - - 45
3.2.2 Attempts at the Reaction of Benzotriazole with Aliphatic Thioamides and Aldehydes - 52
3.2.3 Reaction of Benzotriazole, Benzaldehyde, and Thiobenzamide - 52
3.2.4 Reduction of N-[1-(Benzotriazol-1-yl)alkyl]-thioamides with Sodium Borohydride - - - - - - - - - - - - - - - - - 54
3.2.5 Reaction of Adducts (**3.10**) with Grignard Reagents - - - - - - - 56
3.3 Conclusions - 60
3.4 Experimental - 60
3.4.1 General Procedure for Preparation of N-[1-Benzo-triazol-1-yl)alkyl]thioamides (**3.10**)-(**3.12**) - - - - - - - - - - - - - 60
3.4.2 General Procedure for Reduction of Adducts (**3.10**) and (**3.11**) with Sodium Borohydride - - - - - - - - - - - - 65
3.4.3 General Procedure for Preparation of Secondary Thioamides by Reaction of Adducts (**3.10**) with Grignard Reagents - - - - - 67

IV N-FUNCTIONALIZATION OF HETEROCYCLES *VIA* LITHIATION AND ELECTROPHILIC SUBSTITUTION - - - - - - - - - - - - - - - - - - - 71

4.1 Introduction - 71
4.1.1 General Overview on the Formation and Stabi-lity of α-Heterocarbanions - 71
4.1.2 Activation of the α-Methylene Protons by a Heterocyclic Moiety - 72
4.1.3 Acidity Measurements for Protons in Heterocyclic Rings - - - - 75
4.1.4 Aim of the Work - 78
4.2 Results and Discussion - 80
4.2.1 Preparation of N-(Benzotriazol-1-ylmethyl) Heterocycles (**4.2**) - 80
4.2.2 Reactions of Lithiated Indole and Carbazole Adducts (**4.2.1**) and (**4.2.2**) with Electrophiles - - - - - - - - - - 82
4.2.2.1 Esters as Electrophiles - - - - - - - - - - - - - - - - - - - 83
4.2.2.2 Aliphatic and Aromatic Aldehydes as Electrophiles - - - 85
4.2.2.3 Benzyl Bromide as an Electrophile - - - - - - - - - - - - 87
4.2.3 Lithiation of Benzimidazole and Imidazole Derivatives and Consequent Reaction with Electrophiles - - - - - - - - - - - 89
4.2.4 Attempted Removal of Benzotriazole - - - - - - - - - - - - - - - 93
4.2.5 Reduction of Acyl and Aroyl Derivatives of Indole and Carbazole with Sodium Borohydride - - - - - - - 95
4.3 Conclusions - 98

4.4 Experimental ---------- 99
4.4.1 General Procedure for Preparation of N-(Benzotriazol-1-ylmethyl) Heterocycles ---------- 99
4.4.2 General Procedure for Lithiation of Adducts (**4.2**) and Reaction with Electrophile ---------- 102
4.4.3 General Procedure for Reduction of Acyl and Benzoyl Adducts of Indole and Carbazole with $NaBH_4$ ---------- 109

V REACTIVITY OF 1-TRIMETHYLSILYLBENZOTRIAZOLE ---------- 113

5.1 Introduction ---------- 113
5.1.1 Physical Properties of Silicon ---------- 113
5.1.2 Silylation of Organic Compounds ---------- 113
5.1.3 Reactivity of the Nitrogen-Silicon Bond ---------- 114
5.1.4 Aim of the Work ---------- 115
5.2 Results and Discussion ---------- 117
5.2.1 Reaction of 1-Trimethylsilylbenzotriazole with Aliphatic and Aromatic Aldehydes ---------- 117
5.2.2 Attempts at Lithiation and Addition of Electrophile to (**5.5**) -- 118
5.2.3 Reaction of 1-Trimethylsilylbenzotriazole with Other Electrophiles ---------- 119
5.2.4 Reactivity of 1-Trimethylsilyloxy-3-(benzotriazol-1-yl)-1-cyclohexene Towards Electrophiles ---------- 120
5.2.4.1 Acid Hydrolysis ---------- 121
5.2.4.2 Reactions with Alkyl Halides, Halogens, Acid Chlorides, and Aldehydes ---------- 124
5.3 Conclusions ---------- 129
5.4 Experimental ---------- 129

VI N-MONOMETHYLATION OF PRIMARY AMINES *VIA* INTERMEDIATE BENZOTHIAZOL-2(3*H*)-IMINES ---------- 136

6.1 Introduction ---------- 136
6.1.1 Reactivity of 2-Mercaptobenzothiazole Derivatives Towards Nucleophiles ---------- 136
6.1.2 General Methods for N-Monoalkylation of Primary Amines -- 138
6.1.3 Aim of the Work ---------- 139
6.2 Results and Discussion ---------- 141
6.2.1 Formation of 3-Methylbenzothiazol-2(3*H*)-Imines (**6.3**) ----- 141
6.2.2 Methylation of the Imine Nitrogen in Compounds (**6.3**) ----- 143
6.2.3 Preparation of N-Monomethylated Amines (**6.6**) ---------- 145
6.3 Conclusions ---------- 147
6.4 Experimental ---------- 147
6.4.1 General Procedure for the Preparation of N-Methylbenzothiazoline-2-imines (**6.3**) ---------- 148
6.4.2 General Procedure for the Methylation of Imines (**6.3**) ----- 150
6.4.3 General Procedure for the Preparation of N-Methylated Amines (**6.6**) ---------- 153

VII SUMMARY ---------- 156

BIBLIOGRAPHY ---------- 159

BIOGRAPHICAL SKETCH ---------- 176

Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

SOME APPLICATIONS OF BENZOTRIAZOLE
AS A SYNTHETIC AUXILIARY

by

Malgorzata Drewniak-Deyrup

December, 1988

Chairman: Alan R. Katritzky
Major Department: Chemistry

The synthetic utility of two heterocyclic molecules, benzotriazole and benzothiazole was studied.

Benzotriazole, a good leaving group, has been used to develop several synthetic transformations involving carbon-carbon bond formation in compounds containing nitrogen functionality. The facile reaction between benzotriazole, aldehyde, and nitrogen functionality in amides and thioamides led to formation of the (1:1:1) adducts. These amide and thioamide adducts were then easily transformed into the N-monoalkylated amides or thioamides with simultaneous expulsion of benzotriazole using sodium borohydride or Grignard reagents.

The adducts formed from 1-chloromethylbenzotriazole and NH-heterocycles were stable to these reagents, but they could be easily lithiated. The presence of the benzotriazole moiety directed the site of metallation and stabilized the carbanion formed. However, the elimination of benzotriazole was, in this case, unsuccessful.

The reactivity of 1-trimethylsilylbenzotriazole toward aldehydes and α,β-unsaturated ketones was investigated. 1-Trimethylsilylbenzotriazole underwent 1,4-addition to the α,β-unsaturated ketones to give silyl enol ethers, which were easily hydrolyzed to the corresponding ketones.

Primary aliphatic and aromatic amines were exclusively monomethylated on nitrogen, in high yield under mild conditions, by successive treatment with (1) 3-methyl-2-methylthiobenzothiazolium iodide, (2) methyl iodide or p-toluenesulphonate, and (3) butylamine.

CHAPTER I
GENERAL INTRODUCTION

1.1 General View of the Physical and Chemical Properties of Benzotriazole and Its Applications

Benzotriazole (**1.1**) belongs to a class of heterocyclic compounds derived from 1*H*-1,2,3-triazole. This triazole moiety includes two carbons and three adjacent nitrogen atoms built into a five-membered, aromatic ring. One important feature of the benzotriazole structure is the strong electron-withdrawing character of the nitrogen-nitrogen double bond. This feature is reflected in the higher acidity of benzotriazole (pK_a 8.38) [88JA(110)4105]. In comparison, similar heterocyclic systems containing fused five-membered rings like pyrrole (pK_a 23) [81JOC(46)632], carbazole (pK_a 19.9) [81JOC(46)632] or benzimidazole (pK_a 13.2) [58JCS1974] are less acidic.

Studies of the charge distribution in the benzotriazole anion (Figure 1.1) based on

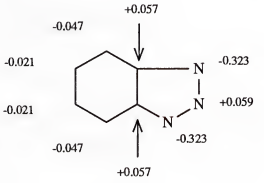


Figure 1.1

INDO semi-empirical calculations [75JCS(P2)1695] indicated that most of the negative charge is on the N-1 and N-3. Molecular orbital calculations more recently [78JHC(15)127] gave different values (Figure 1.2), but also showed higher electron density on N-1 and N-3. In agreement with these calculations conjugate additions of

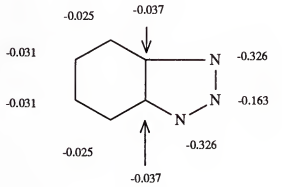
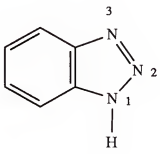


Figure 1.2

benzotriazole to acrylic acid, acrylonitrile, acrylamide, crotonic acid, cinnamaldehyde, or benzalacetophenone all gave 1-benzotriazole derivatives [54JA(76)4933].

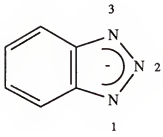
Similarly, formaldehyde and benzotriazole formed 1-hydroxymethylbenzotriazole [52JA(74)3868, 55JA(77)5386]. An analogous product resulted when p-nitrobenzaldehyde was used [54JA(76)4933]. In reactions with formaldehyde and amines, benzotriazole yielded Mannich bases with substituents at the 1-position [52JA(74)3868, 55JA(77)5386]. Recent studies have shown that these bases exist in solution as equilibrium mixtures of 1- and 2-isomers [87JCS(P1)2673] (see Section 1.3).

Benzotriazole and its derivatives have found their way into many important industrial applications. It is well known that benzotriazole (**1.1**) is an important corrosion inhibitor for copper, copper alloys and other metals. Benzotriazole is strongly adsorbed on metal surfaces and produces protective surface films. Several investigations have been carried out on the nature of these protective layers [63MI69, 67MI1, 70MI9, 70MI359, for a review see 83MI109].



(BTAH)

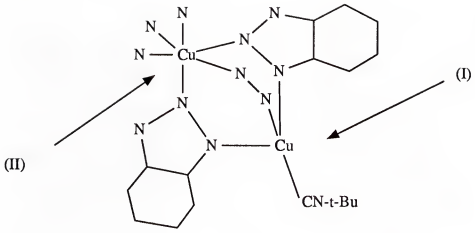
(1.1)



(BTA)

(1.1a)

It is now known that benzotriazole is a very versatile ligand. Both neutral benzotriazole (**1.1**) $[Cu(BTHA)_2Cl_2]$ [79IC(18)1947] and its deprotonated (**1.1a**) form $[Ir(CO)(PPh_3)_2(BTA)]$, $[Zn_2(BTA)_4]_n$ [81ACS(A)733, 739] serve as ligands. Several metal complexes have been found in which more than one benzotriazole nitrogen acts in a donor capacity [78IC(17)3026, 78IC(17)3711, 81JA(103)211]. Bridging coordination using N-1, N-2, and N-3 has been recently established in mixed-valence cluster compounds such as $Cu_5(BTA)_6(t\text{-}C_4H_9NC)_4$ [81JA(103)211] (Figure 1.3), Tl(BTA) [79IC(18)1947], and $Cu_5(BTA)_6(acac)_4$ [78IC(17)3711]. As shown on Figure 1.3, benzotriazolate anions can bridge multiple sites containing both copper (I) and copper (II).



$Cu_5(BTA)_6(t\text{-}C_4H_9NC)_4$

(only two BTA ligands are shown, and multiple bonds are not indicated)

Figure 1.3

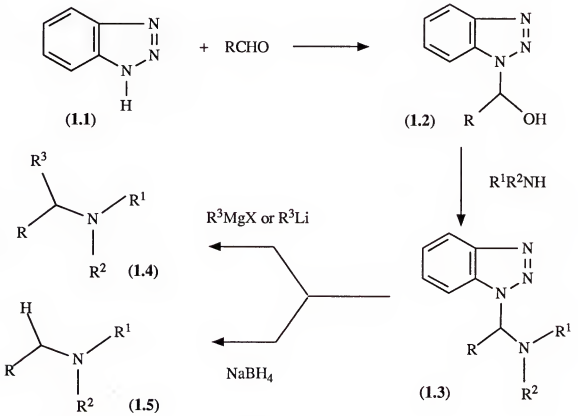
Benzotriazole and its derivatives are used in the polymer industry as additives to photopolymerizable paints, as well as in insulating and lubricating oils. Benzotriazole derivatives have found numerous applications as fluorescent compounds [81HCA662], photostabilizers [70JHC(7)1113, 72PAC(30)135], and as biologically active components [68MI1814, 78MI63, 80MI291, 82MI167, 82MI328]. Both 5- and 6-chloro-1-aroylbenzotriazoles revealed antiinflammatory activities [80JHC(17)1505].

1.2 Benzotriazole as a Synthetic Auxiliary

The strong electron-withdrawing character of its heterocyclic ring makes benzotriazole a unique system that has been utilized in many synthetic transformations. Benzotriazole has served as an activating group in the formation of new carbon-carbon

bonds [87JCS(P1)781]. The benzotriazole moiety could then be easily removed to release a target molecule. This cleavage could be facilitated by quaternization on N-3 [87JCS(P1)781].

Previous work by Katritzky *et al.* [87JCS(P1)781-819] explained many applications of benzotriazole as a synthetic auxiliary. Benzotriazole reacted easily with aldehydes to form hydroxyalkyl derivatives (Scheme 1.1). These derivatives reacted subsequently with aromatic and heterocyclic amines to give the corresponding N-substituted aminoalkyl adducts. The products were easily converted to N-monoalkylated aro-



Scheme 1.1

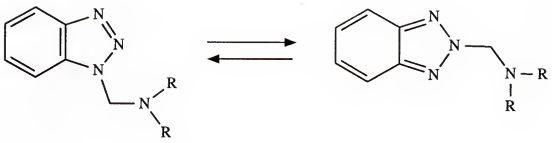
matic and heteroaromatic amines upon treatment with nucleophiles such as sodium borohydride, Grignard reagents [JCS(P1)799, 805] or organolithium reagents [84TL1635] (Scheme 1.1).

Benzotriazole was also shown to react in one pot with aldehydes and different nitrogen functionalities (like secondary amines, hydroxylamines [88JCS(P1)IP1], and sulfonamides [88UP1]). All of the products were susceptible to nucleophilic attack. The strong electron-withdrawing heterocyclic ring destabilized the bond between the heterocyclic nitrogen and the carbon atom and thus facilitated displacement of the benzotriazole moiety to yield (**1.4**) or (**1.5**). This three-step sequence led to N-monoalkylated derivatives of amines, hydroxylamines, and sulfonamides.

1.3 The Phenomena of 1- and 2-Substituted Benzotriazoles

Although, according to quantum mechanical calculations, most of the negative charge is localized on N-1 and N-3, many products in which benzotriazole is substituted at N-2 have been synthesized. The 2-substituted derivatives are usually minor products. Classical methods for the preparation of benzotriazoles such as cyclization of 1,2-azoaminobenzenes [21CB(54)2191,2201], or thermal decomposition of o-azidobenzenes [68JOC(33)2954] can be applied to syntheses of pure 2*H*-isomers.

An interesting facet of benzotriazole is the isomerism of its 1- and 2-substituted derivatives. N-(Dialkylaminomethyl)benzotriazoles have been shown [75JCS(P1)1181] to exist in solution as an equilibrium mixture of 1- and 2-isomers. Katritzky and coworkers carried out exhaustive studies on the mechanism of interconversion [87JCS(P1)2673] (Scheme 1.2). These studies used ^{1}H, ^{13}C NMR, IR, and X-ray crystallography to demonstrate that these compounds exist only as 1-(N,N-disubstituted aminomethyl)benzotriazoles in the solid state. An equilibrium mixture (with the 1-isomer predominating) was

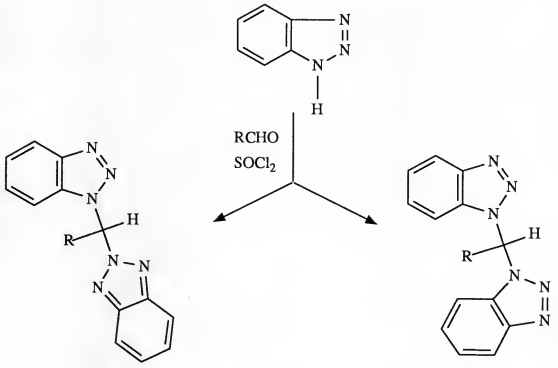


Scheme 1.2

found in the melt, in an argon matrix and in solution (Scheme 1.2). The authors showed that, in solution, the amount of 1-isomer relative to the 2-isomer increased with the polarity of the solvent, whereas increasing bulkiness of the N-aminomethyl substituent favored 2-substitution. The mechanism of isomerization was studied by means of cross-over experiments and NMR measurements. The authors concluded that the mechanism is intermolecular and proceeds *via* dissociation into imminium ions and the benzotriazole anion.

The presence of two isomers has also been observed in some further studies of benzotriazole derivatives [87JCS(P1)811]. Reaction of 2 mol equivalents of benzotriazole, 7 mol equivalents of an aliphatic or aromatic aldehyde, and an excess of thionyl chloride yielded a mixture of 1,1-bis(benzotriazol-1-yl)alkanes or bis(benzotriazol-1-yl)methylarenes and 1-(benzotriazol-1-yl)-1-(benzotriazol-2-yl)alkanes or (benzotriazol-1-yl)(benzotriazol-2-yl)methylarenes (Scheme 1.3). These isomers could be separated by column chromatography. The 1,1-adduct was always the major product, and, in the case of aromatic aldehydes, the amount of the 1,2-adduct was very small. These 1,1- and 1,2-isomers could be easily distinguished by spectroscopic methods.

Prolonged reflux of 1,1- or 1,2-adducts in thionyl chloride gave only small amounts of the other isomer. This result clearly showed that the rate of equilibrium between these two isomers was very small. Other examples of 1- and 2-substituted derivatives of benzotriazole will be discussed in Chapter III.



Scheme 1.3

CHAPTER II
N-MONOALKYLATION OF PRIMARY AMIDES USING BENZOTRIAZOLE

2.1 Introduction

The amide moiety is an important constituent of many biologically significant compounds, including polypeptides and proteins. Many amide derivatives exhibit pharmacological activity. Therefore, in the preparation of novel amides, the alkylation of already existing amides to give more substituted analogues has attracted much attention. The N-alkylation of amides has also been used as an intermediate step in the synthesis of secondary and tertiary amines that have different alkyl substituents [76CSR(5)23].

2.1.1 General Methods for Preparation of N-Alkylated Amides

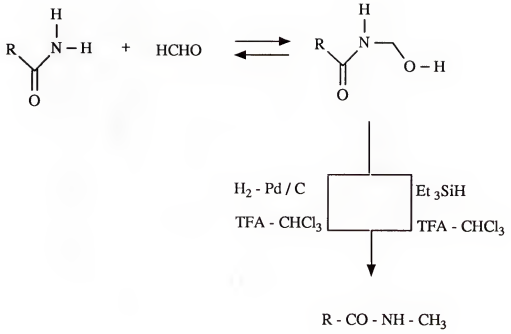
The neutral amide group, in general [83JCS(P2)1037], is regiospecifically alkylated at the carbonyl oxygen atom [79TL4671, 83T(39)433] and indeed amides are protonated on oxygen [61CI(L)722]. Amide anions usually react with electrophiles at the nitrogen atom, and in fact, the reaction of amide anions with alkyl halides has frequently been used for their alkylation. However, methods reported in the literature usually require the use of a strong base (often in large excess) such as potassium hydroxide in water [1877CB(10)327], in ethanol [1887CB(20)3422], or in dimethyl sulfoxide [71S266, 79T(35)2169]. Other methods using sodium metal, sodium hydride or sodium hydroxide in inert solvents such as toluene or xylene [49JOC(14)1099, 52JA(74)1010], need drastic reaction conditions and result in variable yields and impure products. Phase transfer

catalysis using sodium hydroxide in benzene has been successful for monoalkylation of both unsubstituted [81S1005] and monosubstituted amides [79S527] in good yields, although dialkylated products were isolated with more reactive alkyl halides. The most successful N-alkylation of amides with alkyl halides is that reported by Sukata [85BCJ(58)838] using potassium hydroxide on alumina at 60°C. Recently, Shono and coworkers [86CL425] reported an electroreductive procedure that gave good yields for N-monoalkylation using alkyl halides; however, the method was only applied to secondary amides.

The reaction of secondary and primary mono-, di-, and poly-amides with potassium t-butoxide and an active alkene such as p-tolyl vinyl sulfone resulted in formation of disubstiututed amides in moderate to low yields. The Michael reaction of amides with electrophilic alkenes, such as acrylonitrile, represents a specialized type of N-alkylation [76JCS(P1)1543].

The use of reagents other than alkyl halides to substitute amides is rare. Watanabe *et al.* have reported N-alkylation of amides with alcohols at 180°C using ruthenium complexes as catalysts [83BCJ(56)2647]. In this process, however, the yields and the selectivities for N-monoalkylation were usually low.

Formaldehyde reacts with amides to give methylol derivatives. These products can be reduced to N-methylamides with triethylsilane - TFA or by catalytic hydrogenation at atmospheric pressure in the presence of TFA [76JOC(41)725] (Scheme 2.1). No N-alkylations of amides by other aldehydes have been reported with the exception of a brief note without experimental detail [62JOC(27)2205]. The authors described a procedure for N-alkylation of acetamide using a mixture of acetal, sulfuric acid, trifluoroacetic acid, and acetic acid, with catalytic amount of palladium on charcoal in hydrogen atmosphere.

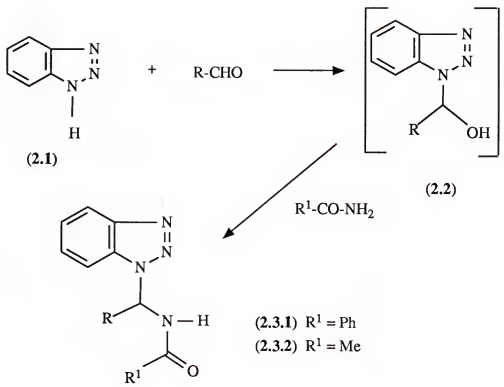


Scheme 2.1

Two products were obtained: N-ethyl- and N-propyl-acetamide in 50% yield. Methylation of amides by reaction with chloromethyl methyl sulphide in strong acid, followed by reduction with Raney nickel has been reported [75CC320], but again no experimental details were given.

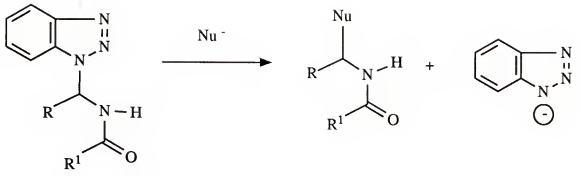
2.1.2 Aim of the Work

The goal of this project was to develop a method of considerable generality for N-monoalkylation of primary amides using common reagents. Previous work of Katritzky *et al.* [87JCS(P1)781] with benzotriazole had shown that this heterocyclic system reacts easily with amines and aldehydes to form N-aminoalkylbenzotriazoles. By analogy, benzotriazole, an aldehyde, and an amide should react to form the corresponding 1:1:1 adduct (Scheme 2.2).



Scheme 2.2

These adducts (**2.3**) could be used for further synthetic transformations. Benzotriazole is known to be a good leaving group [87JCS(P1)791] because of its electron-withdrawing character. The methine carbon in these adducts (**2.3**) should be, therefore, activated toward simple nucleophiles, like hydrides, Grignard reagents, cyanides or alkoxides. The incoming nucleophile, under mild reaction conditions, should displace the benzotriazole and form a bond with the methine carbon (Scheme 2.3). If successful, the sum of Schemes 2.2 and 2.3 would constitute a new strategy for selective substitution on the nitrogen of amides. This approach would avoid the use of alkylating agents.



(2.3) **(2.4)**

Nu = H^-, R^2MgX, CN^-, RO^- etc.

Scheme 2.3

2.2 Results and Discussion

2.2.1 Formation of Adducts (2.3.1) and (2.3.2)

In a one pot reaction, benzotriazole (**2.1**), an aldehyde, and an amide in equimolar amounts were refluxed in dry toluene for 24-48 hours. The reaction probably involves the formation of a hydroxyalkylbenzotriazole intermediate (**2.2**) which subsequently reacts with the amide (Scheme 2.2). The water formed as a side product was removed azeotropically with toluene. This procedure was successful for aliphatic or aromatic aldehydes and amides on 0.1 molar scale. Details are given in Table 2.1.

Table 2.1 Preparation of N-[1-(Benzotriazol-1-yl)alkyl]amides (**2.3.1**) and (**2.3.2**)

Compound	R of RCHO	$R^1$of R^1CONH_2	Time (hours)	Yield (%)	Recryst. solvent	M.p. (°C)
(2.3.1.1)	H	Ph	24	78	MeOH	177-179
(2.3.1.2)	Pr^i	Ph	24	52	MeOH	191-193
(2.3.1.3)	Pr^n	Ph	24	59	MeOH	156-159
(2.3.1.4)	$Pent^n$	Ph	48	48	MeOH	110-115
(2.3.1.5)	Oct^n	Ph	48	74	MeOH	102-105
(2.3.1.6)	Ph	Ph	24	60	MeOH	188-190
(2.3.2.1)	Pr^i	Me	48	51	Benzene	164-167
(2.3.2.2)	Ph	Me	48	45	Benzene	174-177
(2.3.2.3)	p-Tolyl	Me	40	42	Benzene	186-188

The structures of all the adducts were proved by their spectral properties. In the ^{13}C NMR spectra of the adducts (**2.3.1**) and (**2.3.2**), the chemical shifts of the carbons of the benzotriazole ring (Table 2.2) corresponded closely to those previously reported for other 1-substituted benzotriazoles [83H(20)1787]. Figure 2.1 given below shows the proper numbering of the carbons in the benzotriazole ring. Carbons C-7 and C-7a appeared at δ 111.2-109.6 ppm and δ 132.2-131.1 ppm. Carbons C-3a and C-4 were slightly shielded and occurred at δ 145.4-144.3 ppm and δ 119.3-118.3 ppm. Signals at δ 124.2-122.9 ppm and δ 127.7-126.2 ppm were attributed to C-5 and C-6 carbons respectively. The chemical shifts of the carbonyl carbons for compounds (**2.3.1**) and (**2.3.2**) fell in the region 170.8-166.7 ppm.

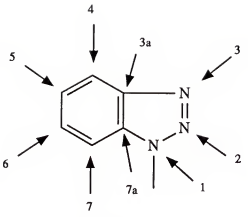


Figure 2.1

Table 2.2 ^{13}C NMR Chemical Shifts of the Carbonyl and Benzotriazole Carbons in Compounds (**2.3.1**) and (**2.3.2**)

Adduct	C=O	C-3a	C-4	C-5	C-6	C-7	C-7a	NCHR
(2.3.1.1)	166.9	145.4	118.9	123.8	127.2	111.2	132.2	51.7[a]
(2.3.1.2)	166.9	145.0	119.0	123.7	127.2	111.0	132.0	69.6
(2.3.1.3)	166.7	145.2	119.1	123.9	127.1	111.1	132.0	63.8
(2.3.1.4)	167.4	145.3	119.2	124.2	127.7	110.5	132.0	62.7
(2.3.1.5)	167.3	145.4	119.3	124.2	127.7	110.5	132.8	62.7
(2.3.1.6)	166.9	145.3	119.2	123.9	127.3	111.1	132.0	66.0
(2.3.2.1)	170.8	145.0	119.2	124.1	127.6	110.2	133.2	67.8
(2.3.2.2)	169.7	145.3	118.9	123.5	126.9	110.4	131.8	65.0
(2.3.2.3)	169.3	144.5	118.3	122.9	126.2	109.6	131.1	64.0

[a]The chemical shift of the methylene group.

As expected, the peak corresponding to the methine carbon CH-α between the heterocyclic ring and amide nitrogen appeared at δ 69.6-51.7 ppm (Table 2.2). In addition, the ^{13}C NMR spectra of the adducts (**2.3.1**) showed four signals corresponding to the aromatic carbons of benzamide (Figure 2.2). Compared to the ^{13}C NMR chemical shifts in unsubstituted benzamide [78MI189], the quaternary carbon C-1'' was slightly deshielded (1.6-1.1 ppm); the other carbons were little affected (Table 2.3). In (**2.3.2**) the acetamide methyl group resonated at δ 22.5-21.3 ppm [83MI343]. The aliphatic carbons of the R substituents of the adducts (**2.3.1**) displayed ^{13}C NMR spectra patterns that were very similar to aliphatic amines published elsewhere [78MI190].

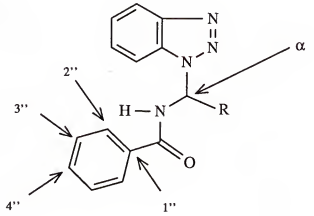


Figure 2.2

In the ^{1}H NMR spectra of compounds (**2.3.1**) and (**2.3.2**), the most deshielded proton has been assigned to H-4 of the benzotriazole [83H(20)1787]. The aromatic protons of benzotriazole and the phenyl substituents gave rise to complex multiplets between δ 8.15 and 7.13 ppm. The NH proton resonated downfield at δ 10.25-9.79 ppm and appeared as a doublet with a coupling constant in the range 8 to 9 Hz. The splitting

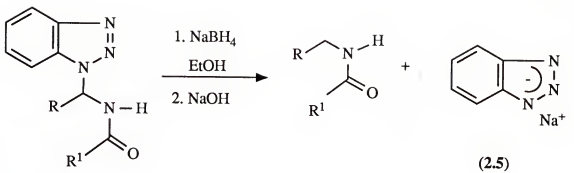
Table 2.3 ^{13}C NMR Chemical Shifts of Benzamide Carbons in Compounds (**2.3.1.1**)-(**2.3.1.6**)

Compound	C-1''	C-2''	C-3''	C-4''
(**2.3.1.1**)	132.8	127.4	128.2	131.7
(**2.3.1.2**)	133.1	127.6	128.1	131.6
(**2.3.1.3**)	133.1	127.6	128.2	131.7
(**2.3.1.4**)	133.1	127.4	128.3	131.9
(**2.3.1.5**)	133.1	127.4	128.4	132.0
(**2.3.1.6**)	132.9	127.9	128.6	131.8

was due to the adjacent α-methine proton. This CH proton was significantly deshielded to δ 7.04-6.26 ppm due to the effect exerted by the benzotriazole ring. Protons attached to C-β gave rise to an obscure multiplet in the region δ 3.49-2.45 ppm. The other aliphatic protons of the aliphatic substituent R appeared upfield as complex multiplets. The chemical shifts of two nonequivalent methyl groups in the isopropyl substituent in compounds (**2.3.1.2**) and (**2.3.2.1**) differed by about 0.5 ppm and appeared as sharp doublets with coupling constants of 6 and 7 Hz., respectively.

2.2.2 Reaction of Adducts (**2.3.1**) and (**2.3.2**) with Sodium Borohydride

The adducts (**2.3**) described in Section 2.2.1 were readily reduced by sodium borohydride (excess) in absolute ethanol. Benzotriazole was eliminated as a sodium salt (**2.5**) and N-alkylated amides (**2.6**) formed in excellent yields (Scheme 2.4).



(2.3.1) R^1 = Ph
(2.3.2) R^1 = Me

(2.6.1) R^1 = Ph
(2.6.2) R^1 = Me

(2.5)

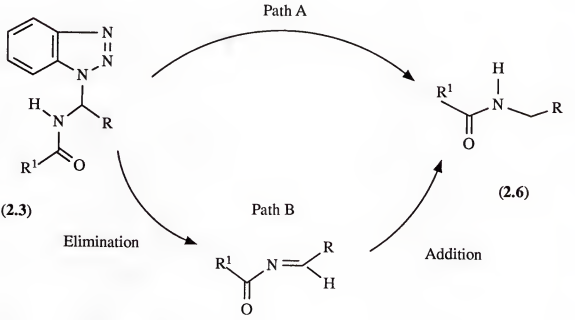
Scheme 2.4

The N-monoalkylamide products were identified by their spectral data and comparison of the melting points with literature values (Table 2.4).

Table 2.4 Preparation of N-Monoalkylated Amides (**2.6**)

Amide	R	R^1	Yield (%)	M.p. (°C)	Lit.m.p. (°C)	Reference
(2.6.1.1)	H	Ph	96	75-77	78	02JA(24)758
(2.6.1.2)	Pr^i	Ph	96	55-57	55-58	01JCS(L)391
(2.6.1.3)	Pr^n	Ph	96	69-71	68-70	22CB(55)3165
(2.6.1.4)	$Pent^n$	Ph	97	55-58	56.5-57	62MI853
(2.6.1.5)	Oct^n	Ph	99	48-50	49	11CB(44)1464
(2.6.1.6)	Ph	Ph	94	104-105	105-106	82MI604
(2.6.2.1)	Ph	Me	98	58-60	61	84MI66

One could propose two possible mechanisms for the reduction shown in Scheme 2.4. Direct displacement of the benzotriazole moiety could proceed through an S_N2 like mechanism (path A). Alternatively, the product could be formed *via* a two-step (path B) elimination-addition route (Scheme 2.5). The elimination step in path B could be



Scheme 2.5

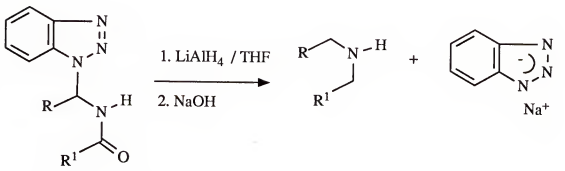
initiated either by elimination of benzotriazole from the alpha carbon or abstraction of the proton from amide nitrogen. Both paths would produce the same N-acylimine intermediate, which would be susceptible to hydride addition.

The ^{13}C NMR spectra of N-alkylated amides **(2.6.1)** and **(2.6.2)** in many respects resembled those of the parent adducts: no significant changes were observed in the chemical shifts of the C=O or the carbons of the substituents R and R^1. The principal differences were in the chemical shifts of the characteristic C-α carbon. In the absence of

the benzotriazole, that C-α was shifted upfield into the δ 47.3-26.6 ppm region. In the ^{1}H NMR spectra of the amides, the most significant difference was observed for the protons attached to C-α; the chemical shifts were moved upfield into the δ 4.55-2.93 ppm region.

2.2.3 Reaction of Adducts (**2.3.1**) and (**2.3.2**) with Lithium Aluminum Hydride

Some of the adducts were also subjected to reduction by lithium aluminum hydride (Scheme 2.6) to give the expected secondary amines (**2.7**). These reduction products were



(**2.3.1**) R^1 = Ph
(**2.3.2**) R^1 = Me

(**2.7.1**) R^1 = Ph
(**2.7.2**) R^1 = Me

(**2.5**)

Scheme 2.6

pure by TLC and ^{1}H NMR. The identity of these secondary amines was confirmed by their spectral properties (IR, ^{1}H, and ^{13}C NMR) and molecular formula determinations by GC-MS (Table 2.5). In the ^{1}H NMR spectra of the secondary amines (**2.7.1**), the characteristic methylene protons attached to the phenyl ring appeared as a singlet at δ 3.75-3.69 ppm, whereas the doublet at δ 2.61-2.40 ppm corresponded to the protons attached to C-α for compounds (**2.7.1.2-2.7.1.5**). The ^{13}C NMR spectra of N-alkylated amines showed some similarities to those of the corresponding adducts. The reduced

carbonyl carbon appeared as a methylene carbon at δ 57.2-53.0 ppm and the C-α resonated at δ 53.7-35.6 ppm.

Table 2.5 Preparation of Secondary Amines (**2.7.1**) and (**2.7.2**)

Amine	R	R^1	Yield (%)	M^+ Calc.	M^+ Found
(**2.7.1.1**)	H	Ph	76	121.0891	121.0882
(**2.7.1.2**)	Pr^i	Ph	75	163.1360	163.1367
(**2.7.1.3**)	Pr^n	Ph	58	163.1360	163.1361
(**2.7.1.4**)	$Pent^n$	Ph	66	191.1661	191.1668
(**2.7.1.5**)	Oct^n	Ph	64	233.2143	233.2154
(**2.7.1.6**)	Ph	Ph	65	197.1204	197.1193
(**2.7.2.1**)	Ph	Me	83	135.1047	135.1045

In the IR spectra of compounds (**2.3**), (**2.6**), and (**2.7**), the characteristic N-H stretching and N-H bending vibrations were observed at 3310-3265 cm^{-1} and 1600-1525 cm^{-1} respectively. Compounds (**2.3**) and (**2.6**) showed the characteristic medium to strong absorption for the amide carbonyl group in the 1670-1635 cm^{-1} region.

2.2.4 Reactions of Adducts (2.3) with Grignard and Organolithium Reagents

Preparation of sterically hindered amides by deprotonation at the methylene group alpha to the amide nitrogen (Figure 2.3) with a strong base, followed by reaction with electrophiles has been reported by Tischler [78TL3] and by Beak [78CR275, 84CR471].

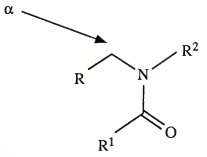
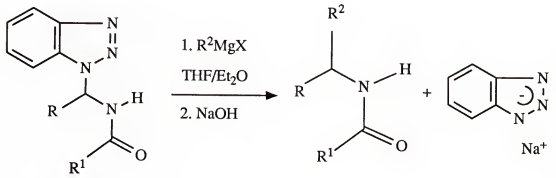


Figure 2.3

No alternative strategy for the construction of the C-C bond of amides by reaction with a nucleophilic alkylating agent at the carbon alpha to the amide nitrogen has been reported in the literature. The amidoalkyl derivatives of benzotriazole (**2.3**) reacted with 2.1 equivalents of a Grignard reagent (Scheme 2.7) in a mixture of diethyl ether and



(**2.3**) (**2.8**) (**2.5**)

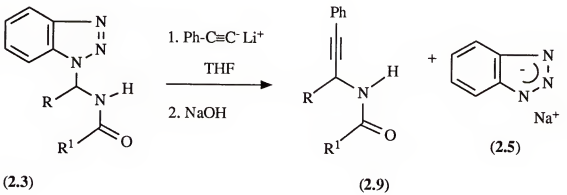
Scheme 2.7

tetrahydrofuran to give branched secondary amides (**2.8**) in very good yields (Table 2.6). Benzotriazole, a side product of the reaction was removed easily as a sodium salt (**2.5**) by extraction in a simple work up.

Table 2.6 Preparation of Secondary Amides (**2.8**) and (**2.9**)

Amide	Starting Adduct	$R^2$of R^2M	Yield (%)	M.p. (°C)	Recryst. solvent
(**2.8.1.1**)	(**2.3.1.2**)	$PhCH_2$	95	146-148	Ethanol(85%)
(**2.8.1.2**)	(**2.3.1.3**)	Ph	92	124-125	Ethanol(85%)
(**2.8.1.3**)	(**2.3.1.5**)	$PhCH_2$	91	117-119	Ethanol
(**2.8.1.4**)	(**2.3.1.6**)	Bu^n	85	129-130	Ethanol(85%)
(**2.8.2.1**)	(**2.3.2.3**)	Ph	93	124-125	EtOAc/P.E.
(**2.9.1.1**)	(**2.3.1.2**)	PhC≡C	81	94-95	EtOAc/P.E.
(**2.9.1.2**)	(**2.3.1.3**)	PhC≡C	86	84-85	Ethanol(85%)

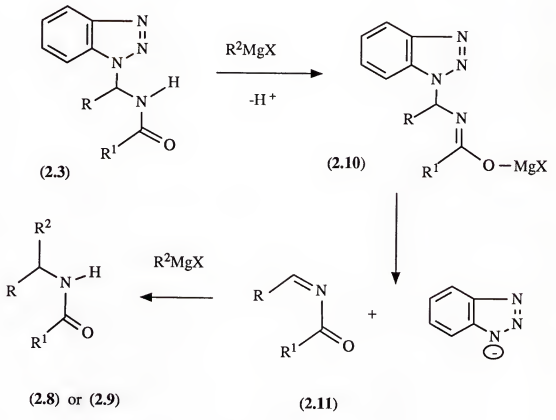
Similarly, the reaction of compounds (**2.3**) with two equivalents of lithium phenyl-acetylide in THF yielded secondary amides (**2.9**) containing an additional functionality (triple bond) β to the nitrogen (Scheme 2.8).



(**2.3**) (**2.9**) (**2.5**)

Scheme 2.8

It is likely that the mechanism of the reaction with nucleophiles proceeds *via* initial deprotonation of the amidoalkylbenzotriazole to give intermediate (**2.10**), which then expels a benzotriazolyl anion to give the acylated imine (**2.11**). The imine is rapidly trapped by the second equivalent of the organometallic reagent to form products (**2.8**) or (**2.9**) (Scheme 2.9).



Scheme 2.9

The structures of all amides synthesized were supported by their analytical and spectral data. The ^{13}C NMR spectra of the secondary amides showed an absorption peak for the carbonyl carbon in the region of δ 168.3-165.5 ppm and for the carbon atom attached to the amide nitrogen atom at δ 56.8-42.3 ppm. Examination of the ^{1}H NMR spectra of these products showed that all contained a doublet at δ 8.8-6.8 ppm for the proton attached to the nitrogen. The proton attached to the tertiary carbon, which appeared in the spectrum as a multiplet at δ 6.12-4.14 ppm, clearly supported the proposed structures of the amides. Both ^{13}C NMR and ^{1}H NMR chemical shifts were in good accordance with literature data for this class of compounds [78MI187, 76OMR536].

The carbonyl frequency of the synthesized amides (amide I band) occurred in the region of 1625-1635 cm^{-1} when examined in the solid state. The amide II band (N-H bending vibrations) at 1570-1520 cm^{-1} is partially under the envelope of the ring vibrations of the phenyl groups. Fine structure usually appeared on the low frequency side of the expected N-H stretching band near 3300 cm^{-1}. This fine structure arises from dimers with a *cis* amide conformation and polymers with a *trans* amide conformation [81MI124].

2.3 Conclusions

The easy formation of benzotriazole amidoalkyl and amidoaryl derivatives thus allows (i) exclusive N-monoalkylation of the primary aliphatic and aromatic amides by reduction of these adducts with sodium borohydride in absolute ethanol; (ii) preparation of α-branched N-monoalkylated amides with the formation of a new C-C bond by reaction of these adducts with Grignard reagents; (iii) formation of secondary amides with additional alkynyl functionalization on the β-carbon to the amide nitrogen; and (iv) synthesis of N-monoalkylated amines by reduction of the adducts with an excess of lithium aluminum hydride in THF. The synthetic route presented above for the alkylation

of primary amides is a general method that leads regioselectively (only on nitrogen) to monoalkylated products. The sequences proceed with good overall yields for both aliphatic and aromatic amides and aldehydes. This new method offers a relatively easy, two-step procedure, applicable on a large scale, and using readily accessible reagents.

2.4 Experimental

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer and only selected absorptions are given. ^1H NMR spectra were obtained on a Varian XL200 (200 MHz, FT mode) spectrometer, with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained on a Varian XL200 (50 MHz) spectrometer referring to the central signal of $CDCl_3$ (77.0 ppm) or Me_2SO-d_6 (39.5 ppm) respectively. Elemental analyses were performed under the supervision of Dr. R. W. King of the Department of Chemistry.

2.4.1 General Procedure for Preparation of N-[1-(Benzotriazol-1-yl)alkyl]amides (**2.3**)

Method A

An amide (0.1 mol), N-hydroxymethylbenzotriazole (14.9 g, 0.1 mol), and 40 ml of dry toluene were refluxed in a Dean-Stark apparatus for the appropriate length of time, and the water collected was removed. Toluene was removed at 60°C/30 mmHg. The residue was treated with 200 ml of diethyl ether, and the resulting solid was recrystallized from the appropriate solvent to give adducts (**2.3**).

Method B

Benzotriazole (11.9 g, 0.1 mol), an aldehyde (0.1 mol), and an amide (0.1 mol) were refluxed for 24-48 hours in 40 ml of dry toluene in a Dean-Stark apparatus. Water (about 1.5 ml) was formed. Toluene was then removed at 60°C/30 mmHg and the residue

was treated with 200 ml of diethyl ether and the resulting solid recrystallized from the appropriate solvent to give adducts of type (**2.3**).

N-[1-(Benzotriazol-1-yl)methyl]benzamide (**2.3.1.1**)

Prepared (78%) from N-hydroxymethylbenzotriazole and benzamide after 24 hours, as a solid, m.p. 177-179°C (needles from methanol) (Found: C, 66.9; H, 4.8; N, 22.2. $C_{14}H_{12}N_4O$ requires: C, 66.7; H, 4.8; N, 22.2%); ν_{max} (nujol) 3300m, 1650s, 1560m cm^{-1}; δ_H (Me_2SO-d_6) 9.89 (1 H, broad, NH), 8.09 (1 H, d, J = 9 Hz, H-4), 7.96-7.13 (8 H, m, other aromatic protons), 6.26 (2 H, d, J = 6 Hz, -CH_2-NH); δ_C (Me_2SO-d_6) 166.9 (C=O), 145.4, 132.8, 132.2, 131.7, 128.2, 127.4, 127.2, 123.8, 118.9, 111.2, 51.7 (N-CH_2).

N-[1-(Benzotriazol-1-yl)-2-methylpropyl]benzamide (**2.3.1.2**)

Prepared (52%) from benzotriazole, isobutyraldehyde, and benzamide after 24 hours, as a solid, m.p. 191-193°C (prisms from methanol) (Found: C, 69.5; H, 6.4; N, 18.9. $C_{17}H_{18}N_4O$ requires: C, 69.4; H, 6.2; N, 19.0%); ν_{max} (nujol) 3300m, 1665m, 1575w cm^{-1}; δ_H (Me_2SO-d_6) 9.79 (1 H, d, J = 8 Hz, NH), 8.19 (1 H, d, J = 7 Hz, H-4), 8.05 (1 H, d, J = 7 Hz, H-7), 7.78-7.40 (7 H, m, other aromatic protons), 6.60 (1 H, d, J = 8 Hz, -CH-NH), 3.49-3.01 (1 H, m, -CH-), 1.27 (3 H, d, J = 6 Hz, -CH_3), 0.67 (3 H, d, J = 6 Hz, -CH_3); δ_C (Me_2SO-d_6) 166.9 (C=O), 145.0, 133.1, 132.0, 131.6, 128.1, 127.6, 127.2, 123.7, 119.0, 111.0, 69.6 (-CH-NH), 31.0, 19.2, 18.4.

N-[1-(Benzotriazol-1-yl)butyl]benzamide (**2.3.1.3**)

Prepared (59%) from benzotriazole, butyraldehyde, and benzamide after 24 hours, as a solid, m.p. 156-159°C (prisms from methanol) (Found: C, 69.4; H, 6.4; N, 18.9. $C_{17}H_{18}N_4O$ requires: C, 69.4; H, 6.2; N, 19.0%); ν_{max} (nujol) 3300w, 1670m, 1525m cm^{-1}; δ_H (Me_2SO-d_6) 9.80 (1 H, d, J = 8 Hz, NH), 8.17 (1 H, d, J = 7 Hz, H-4), 8.07 (1 H, d, J = 7 Hz, H-7), 7.99-7.37 (7 H, m, other aromatic protons), 6.98 (1 H, q, J = 8 Hz, -CH-NH), 2.48-2.45 (2 H, m,-CH_2-2), 1.50-1.21 (2 H, m, -CH_2-3), 0.95 (3 H, t, J = 7 Hz,

-C<u>H</u>$_3$); δ_C (Me_2SO-d_6) 166.7 (C=O), 145.2, 133.1, 132.0, 131.7, 128.2, 127.6, 127.1, 123.9, 119.1, 111.1, 63.8 (-C<u>H</u>-NH), 34.8, 18.4, 13.2.

N-[1-(Benzotriazol-1-yl)hexyl]benzamide (**2.3.1.4**)

Prepared (48%) from benzotriazole, hexanal, and benzamide after 48 hours, as a solid, m.p. 110-115°C (microcrystals from methanol) (Found: C, 70.3; H, 7.0; N, 17.2. $C_{19}H_{22}N_4O$ requires: C, 70.8; H, 6.9; N, 17.4%); ν_{max} (nujol) 3290w, 1665m, 1530m cm^{-1}; δ_H ($CDCl_3$) 9.80 (1 H, d, J = 8 Hz, N<u>H</u>), 8.17 (1 H, d, J = 7 Hz, H-4), 8.14-7.41 (8 H, m, other aromatic protons), 6.92 (1 H, d, J = 8 Hz, -C<u>H</u>-NH), 2.51-2.48 (2 H, m, -C<u>H</u>$_2$-2), 1.60-1.02 (6 H, m, 3 -C<u>H</u>$_2$-), 0.83-0.60 (3 H, m, -C<u>H</u>$_3$); δ_C ($CDCl_3$) 167.4 (C=O), 145.3, 133.1, 132.0, 131.9, 128.3, 127.7, 127.4, 124.2, 119.2, 110.5, 62.7 (-C<u>H</u>-NH), 33.9, 31.0, 25.0, 25.0, 13.5.

N-[1-(Benzotriazol-1-yl)nonyl]benzamide (**2.3.1.5**)

Prepared (74%) from benzotriazole, nonanal, and benzamide after 48 hours, as a solid, m.p. 102-105°C (plates from methanol) (Found: C, 72.2; H, 7.9; N, 15.2. $C_{22}H_{28}N_4O$ requires: C, 72.5; H, 7.7; N, 15.4%); ν_{max} (nujol) 3290w, 1665m, 1530m cm^{-1}; δ_H ($CDCl_3$) 8.19 (1 H, d, J = 9 Hz, H-4), 7.97-7.27 (9 H, m, N<u>H</u> and other aromatic protons), 6.96 (1 H, q, J = 8 Hz, -C<u>H</u>-NH), 2.70-2.36 (2 H, m, -C<u>H</u>$_2$-), 1.90-1.40 (12 H, m, methylene protons), 0.90-0.80 (3 H, m, -C<u>H</u>$_3$); δ_C ($CDCl_3$) 167.3 (C=O), 145.4, 133.1, 132.8, 132.0, 128.7, 128.4, 127.7, 127.4, 124.2, 119.3, 110.5, 62.7 (-C<u>H</u>-NH), 34.0, 31.6, 30.1, 39.0, 28.8, 25.4, 22.5, 14.0.

N-[1-(Benzotriazol-1-ylmethyl)phenyl]benzamide (**2.3.1.6**)

Prepared (60%) from benzotriazole, benzaldehyde, and benzamide after 24 hours, as a solid, m.p. 188-190°C (needles from methanol) (Found: C, 72.9; H, 4.7; N, 16.9. $C_{20}H_{16}N_4O$ requires: C, 73.1; H,4.9; N, 17.1%); ν_{max} (nujol) 3280w, 1650m, 1525m cm^{-1}; δ_H (Me_2SO-d_6) 10.25 (1 H, d, J = 8 Hz, N<u>H</u>), 8.25 (1 H, d, J = 7 Hz, H-4), 8.08-7.36 (14 H,

m, other aromatic protons); δ_C (Me_2SO-d_6) 166.9 (C=O), 145.3, 136.2, 132.9, 132.0, 131.8, 128.6, 128.0, 127.9, 127.3, 126.3, 123.9, 119.2, 111.1, 66.0 (-CH-NH).

N-[1-(Benzotriazol-1-yl)-2-methylpropyl]acetamide (**2.3.2.1**)

Prepared (51%) from benzotriazole, isobutyraldehyde, and acetamide after 48 hours, as a solid, m.p. 164-167°C (prisms from benzene) (Found: C, 61.8; H, 7.1; N, 24.5. $C_{12}H_{16}N_4O$ requires: C, 62.0; H, 6.9; N, 24.1%); ν_{max} (nujol) 3265s, 1675s, 1535m cm^{-1}; δ_H ($CDCl_3$) 8.58 (1 H, d, J = 9 Hz, NH), 8.07 (1 H, d, J = 8 Hz, H-4), 7.87 (1 H, d, J = 8 Hz, H-7), 7.54-7.37 (2 H, m, H-5,6), 6.44 (1 H, d, J = 10 Hz, -CH-NH), 2.91-2.73 (1 H, m, -CH-), 2.03 (3 H, s, -CH_3), 1.23 (3 H, d, J = 7 Hz, -CH_3), 0.77 (3 H, d, J = 7 Hz, -CH_3); δ_C ($CDCl_3$) 170.8 (C=O), 145.0, 133.2, 127.6, 124.1, 119.2, 110.2, 67.8 (-CH-NH), 32.3, 22.5, 18.9. 18.5.

N-[1-(Benzotriazol-1-ylmethyl)phenyl]acetamide (**2.3.2.2**)

Prepared (45%) from benzotriazole, benzaldehyde, and acetamide after 48 hours, as a solid, m.p. 174-177°C (needles from benzene) (Found: C, 67.5; H, 5.3; N, 21.0. $C_{15}H_{14}N_4O$ requires: C, 67.6; H, 5.3; N, 21.0%); ν_{max} (nujol) 3280w, 1645s, 1520m cm^{-1}; δ_H (Me_2SO-d_6) 9.80 (1 H, d, J = 9 Hz, NH), 8.04-7.33 (10 H, m, aromatic protons and -CH-), 2.04 (3 H, s, -CH_3); δ_C (Me_2SO-d_6) 169.7 (C=O), 145.3, 136.2, 131.8, 128.3, 126.9, 126.2, 123.5, 118.9, 110.4, 65.0 (-CH-NH), 21.9.

N-[1-(Benzotriazol-1-ylmethyl)-4-methylphenyl]acetamide (**2.3.2.3**)

Prepared (42%) from benzotriazole, p-methylbenzaldehyde, and acetamide after 40 hours, as a solid, m.p. 186-188°C (needles from benzene) (Found: C, 68.0; H, 5.8; N, 19.6. $C_{16}H_{16}N_4O$ requires: C, 68.5; H, 5.8; N, 20.0%); ν_{max} (nujol) 3280w, 1690s, 1515w cm^{-1}; δ_H ($CDCl_3$) 9.66 (1 H, d, J = 9 Hz, NH), 8.00 (1 H, d, J = 8 Hz, H-4), 7.93 (1 H , d, J = 9 Hz, H-7), 7.48-7.31 (2 H, m, H-5,6), 7.17 (4 H, q, J = 8 Hz, other aromatic protons), 7.03 (1 H, d, J = 8 Hz, -CH-NH), 2.31 (3 H, s, -CH_3), 2.04 (3 H, s, -CH_3); δ_C ($CDCl_3$)

169.3 (C=O) 144.5, 137.4, 132.3, 131.1, 128.1, 126.2, 125.4, 122.9, 118.3, 109.6, 64.0 (-CH-NH), 21.3, 19.8.

2.4.2 General Procedure for Preparation of N-Alkylated Amides (**2.6**)

Compound (**2.3.1**) or (**2.3.2**) (3 mmol) was dissolved in 30 ml of absolute ethanol. Solid sodium borohydride (0.33 g, 9 mmol) was added in one portion, with stirring. The clear solution was refluxed for 3 hours and the solvent was removed at 30°C, on a rotary evaporator. The residue was treated with 30 ml of water and extracted with chloroform (3 x 30 ml). The organic layer was washed with 2N NaOH (30 ml), water (30 ml), and dried with $MgSO_4$ (10 g). The solvent was removed at 20°C on rotary evaporator to afford amides that were pure by TLC and ^1H NMR.

N-Methylbenzamide (**2.6.1.1**)

Prepared (96%) from (**2.3.1.1**) m.p. 75-77°C {lit. m.p. 78°C (ligroine) [02JA(24)758]}; ν_{max} (nujol) 3300s, 1640m, 1540m cm^{-1}; δ_H ($CDCl_3$) 7.82-7.77 (2 H, m, H-2,6), 7.43-7.30 (4 H, m, NH and H-3,4,5), 2.93 (3 H, d, J = 5 Hz, -CH_3); δ_C ($CDCl_3$) 168.4 (C=O), 134.3, 131.0, 128.2, 126.8, 26.6.

N-1-(2-Methylpropyl)benzamide (**2.6.1.2**)

Prepared (96%) from (**2.3.1.2**) m.p. 55-57°C {lit. m.p. 57-58°C (benzene) [01JCS(L)391]}; ν_{max} (nujol) 3290m, 1640s, 1540m cm^{-1}; δ_H ($CDCl_3$) 7.80 (2 H, m, H-2,6), 7.47-7.35 (3 H, m, H-3,4,5), 6.63 (1 H, broad, NH), 3.26 (2 H, t, J = 7 Hz, -CH_2-), 2.00-1.79 (1 H, m, -CH-), 0.95 (6 H, d, J = 7 Hz, 2-CH_3); δ_C 167.7 (C=O), 134.8, 131.2, 128.4, 126.8, 47.3, 28.1, 20.1.

N-(1-Butyl)benzamide (**2.6.1.3**)

Prepared (96%) from (**2.3.1.3**), m.p. 69-71°C {lit. m.p. 68-70°C (benzene) [22CB(55)3165]}; ν_{max} (nujol) 3300s, 1640s, 1535m cm^{-1}; δ_H ($CDCl_3$) 7.81-7.61 (2 H, m,

H-2,6), 7.45-7.32 (3 H, m, H-3,4,5), 6.83 (1 H, broad, NH), 3.45-3.35 (2 H, m, -CH_2-), 1.61-1.31 (4 H, m, 2-CH_2-), 0.91 (3 H, t, J = 7 Hz, -CH_3); δ_C ($CDCl_3$) 167.6 (C=O), 134.7, 131.1, 128.3, 126.8, 39.7, 31.5, 20.0, 13.7.

N-(1-Hexyl)benzamide (**2.6.1.4**)

Prepared (97%) from (**2.3.1.4**), m.p. 55-58°C {lit. m.p. 56.5-57°C (methanol) [62MI853]}; ν_{max} (nujol) 3310m, 1640s, 1540m cm^{-1} ; δ_H ($CDCl_3$) 7.85-7.80 (2 H, m, H-2,6), 7.45-7.27 (4 H, m, NH and H-3,4,5), 3.41-3.31 (2 H, m, -CH_2-), 1.59-1.53 (2 H, m, -CH_2), 1.26-1.25 (6 H, m, 3-CH_2-), 0.85-0.82 (3 H, m, -CH_3); δ_C ($CDCl_3$) 167.5 (C=O), 134.5, 130.7, 128.0, 126.8, 39.9, 31.2, 29.3, 26.4, 22.3 13.7.

N-(1-Nonyl)benzamide (**2.6.1.5**)

Prepared (99%) from (**2.3.1.5**), m.p. 48-50°C {lit. m.p. 49°C (ethanol) [11CB(44)1464]}; ν_{max} (nujol) 3310s, 1640s,1570m cm^{-1}; δ_H ($CDCl_3$) 7.81-7.76 (2 H, m, H-2,6), 7.45-7.28 (3 H, m, H-3,4,5), 6.78 (1 H, broad, NH), 3.45-3.35 (2 H, m, -CH_2-), 1.61-1.55 (2 H, m, -CH_2-), 1.54-1.25 (12 H, m, methylene groups), 0.90-0.84 (3 H, m, -CH_3); δ_C ($CDCl_3$) 167.6 (C=O), 134.7, 131.1, 128.3, 126.8, 40.0, 31.7, 29.5, 29.4, 29.2, 29.1, 26.9, 22.5, 14.0.

N-Benzylbenzamide (**2.6.1.6**)

Prepared (94%) from (**2.3.1.6**), m.p. 104-105°C {lit. m.p. 105-106°C (methanol) [82MI604]}; ν_{max} (nujol) 3310w, 1640w, 1570m cm^{-1}; δ_H ($CDCl_3$) 7.81-7.79 (4 H, m), 7.60-7.24 (6 H, m) all aromatic protons, 7.01 (1 H, broad, NH), 4.55 (2 H, d, J = 7 Hz -CH_2-); δ_C ($CDCl_3$) 167.5 (C=O), 138.2, 134.2, 131.4, 128.6, 128.4, 127.7, 127.3, 126.9, 43.9.

N-Benzylacetamide (**2.6.2.1**)

Prepared (98%) from (**2.3.2.3**), m.p. 58-60°C {lit. m.p. 61°C (benzene) [84MI66]}; ν_{max} (nujol) 3290m, 1635m, 1540m cm^{-1}; δ_H ($CDCl_3$) 7.27-7.16 (6 H, m, all aromatic

protons and NH), 4.28-4.25 (2 H, m, -CH_2-), 1.86 (3 H, s, -CH_3); δ_C ($CDCl_3$) 170.3 (C=O), 128.2, 127.3, 126.9, 43.1, 22.5.

2.4.3 General Procedure for Preparation of N-Alkylated Amines (**2.7**)

Compound (**2.3.1**) or (**2.3.2**) (3 mmol) was dissolved in 30 ml of dry THF. Solid lithium aluminum hydride (0.30 g, excess) was slowly added in three portions with stirring. The resulted suspension was heated for 30 minutes. Ice (1 g) was added to decompose the unreacted lithium aluminum hydride. The solvent was removed at 30°C, on a rotary evaporator. The residue was treated with 2N NaOH (30 ml), and extracted with chloroform (3 x 30 ml). The organic layer was washed with 2N NaOH (30 ml), water (30 ml) and dried with $MgSO_4$ (10 g). The solvent was removed at 20°C, on a rotary evaporator to afford benzylamines pure by TLC and ^{1}H NMR and GC-MS.

N-Methylbenzylamine (**2.7.1.1**)

Prepared (76%) from (**2.3.1.1**) as an oil (Found: M^+, 121.0882, calculated $C_8H_{11}N$: M^+, 121.0891); ν_{max} (neat) 3310w, 1600w cm^{-1}; δ_H ($CDCl_3$) 7.20 (5 H, s, all aromatic protons), 3.69 (2 H, s, -CH_2-), 2.40 (3 H, s, -CH_3), 1.89 (1 H, s, NH); δ_C ($CDCl_3$) 139.7, 128.0, 127.9, 126.6, 55.6 (N-CH_2), 35.6.

N-(2-Methylpropyl)benzylamine (**2.7.1.2**)

Prepared (75%) from (**2.3.1.2**) as an oil (Found: M^+, 163.1367, calculated for $C_{11}H_{17}N$: M^+, 163.1360); ν_{max} (neat) 3300w, 1600w cm^{-1}; δ_H ($CDCl_3$) 7.28-7.26 (6 H, m, all aromatic protons and NH), 3.73 (2 H, s, -CH_2-), 2.40 (2 H, t, J = 7 Hz, -CH_2-), 1.84-1.64 (1 H, m, -CH-), 0.88 (6 H, d, J = 7 Hz, 2 -CH_3); δ_C ($CDCl_3$) 140.4, 128.0, 127.7, 126.5, 57.2 (N-CH_2-), 53.7, 28.1, 20.4.

N-(1-Butyl)benzylamine (**2.7.1.3**)

Prepared (58%) from (**2.3.1.3**) as an oil (Found: M^+, 163.1361, calculated for $C_{11}H_{17}N$: M^+, 163.1360); ν_{max} (neat) 3300w, 1600w cm^{-1}; δ_H ($CDCl_3$) 7.31-7.23 (6 H, m, all aromatic protons and NH), 3.78 (2 H, s, -CH_2-), 2.61 (2 H, t, J = 7 Hz, -CH_2-), 1.83-1.24 (4 H, m, 2 -CH_2-), 0.90 (3 H, t, J = 7 Hz, -CH_3); δ_C ($CDCl_3$) 140.3, 128.2, 127.9, 126.7, 53.7 (N-CH_2-), 48.9, 32.0, 20.3, 13.9.

N-(1-Hexyl)benzylamine (**2.7.1.4**)

Prepared (66%) from (**2.3.1.4**) as an oil (Found: M^+, 191.1668, calculated for $C_{13}H_{21}N$: M^+, 191.1661); ν_{max} (neat) 3300w, 1600w cm^{-1}; δ_H ($CDCl_3$) 7.30-7.20 (5 H, m, aromatic protons), 3.75 (2 H, s, -CH_2-), 2.60 (2 H, t, J = 7 Hz, -CH_2-), 1.56-1.28 (9 H, m, methylene protons and NH), 0.91-0.84 (3 H, m, -CH_3); δ_C ($CDCl_3$) 140.3, 128.0, 127.9, 126.6, 53.9 (N-CH_2-), 49.3, 31.6, 29.9, 26.8, 22.4, 13.8.

N-(1-Nonyl)benzylamine (**2.7.1.5**)

Prepared (64%) from (**2.3.1.5**) as an oil (Found: M^+, 233.2154, calculated for $C_{16}H_{27}N$: M^+, 233.2143); ν_{max} (neat) 3300w, 1600w cm^{-1}; δ_H ($CDCl_3$) 7.31-7.23 (5 H, m, aromatic protons), 3.76 (2 H, s, -CH_2-), 2.60 (2 H, t, J = 7 Hz, -CH_2-), 1.60-1.02 (15 H, m, methylene protons and NH), 0.98-0.97 (3 H, m, -CH_3); δ_C ($CDCl_3$) 140.4, 128.2, 127.9, 126.7, 54.0 (N-CH_2-), 49.4, 31.8, 30.0, 29.5, 29.2, 27.3, 22.6, 14.0.

N-Benzylbenzylamine (**2.7.1.6**)

Prepared (65%) from (**2.3.1.6**) as an oil (Found: M^+, 197.1193, calculated for $C_{14}H_{15}N$: M^+, 197.1204); ν_{max} (neat) 3310w, 1600w cm^{-1}; δ_H ($CDCl_3$) 7.30-7.20 (10 H, m, all aromatic protons), 1.67 (1 H, s, NH), 3.75 (4 H, m, 2 -CH_2-); δ_C ($CDCl_3$) 140.2, 128.2, 127.9, 126.7, 53.0 (N-CH_2-).

N-Ethylbenzylamine (**2.7.2.1**)

Prepared (83%) from (**2.3.2.2**) as a oil (Found: M^+, 135.1045, calculated for $C_9H_{13}N$: M^+, 135.1047); ν_{max} (neat) 3290w, 1600w cm^{-1}; δ_H ($CDCl_3$) 8.32-8.19 (5 H, m, aromatic protons), 2.47 (1 H, s, NH), 4.66 (2 H, s, -CH_2-), 3.62-3.51 (2 H, m, -CH_2-), 2.07-1.09 (3 H, m, -CH_3); δ_C ($CDCl_3$) 140.1, 128.2, 128.0, 126.7, 53.6 (N-CH_2-), 43.3, 14.9.

2.4.4 General Method for Preparation of Secondary Amides by Reaction of Adducts (**2.3.1**) or (**2.3.2**) with Organometallic Compounds

Reaction with Grignard Reagent

Benzotriazole adduct (**2.3.1**) or (**2.3.2**) (5 mmol) in tetrahydrofuran (15 ml) was added dropwise to a Grignard reagent prepared from magnesium turnings (10.5 mmol) and an alkyl or an aryl halide (10.5 mmol) in diethyl ether (20 ml). After addition was completed the reaction mixture was refluxed for 1 hour and then poured onto ice-water (20 g), and NH_4Cl (15 ml, saturated solution). The organic layer was washed with NaOH (2 x 15 ml, 1N), water (2 x 20 ml) and dried with $MgSO_4$ (5 g). Evaporation of the solvent (25°C/35 mmHg) gave the crude product which was then purified.

N-[(α-Benzyl)-2-methylpropyl]benzamide (**2.8.1.1**)

Prepared (95 %) from (**2.3.1.2**) using benzylmagnesium chloride, as a solid, m.p. 146-148°C (needles from 85% ethanol) (Found: C, 80.6; H, 8.1; N, 4.9. $C_{18}H_{21}NO$ requires: C, 80.9; H, 7.9; N, 5.2%); ν_{max} (nujol) 3300m, 1625s cm^{-1}; δ_H (Me_2SO-d_6) 8.04 (1 H, d, J = 9 Hz, NH), 7.75 (2 H, d, J = 7 Hz, H-2,6 of the benzamide ring), 7.42-7.10 (8 H, m, other aromatic protons), 4.14 (1 H, m, -CH-NH), 2.87-2.80 (2 H, m, -CH_2-Ph), 1.94-1.84 (1 H, m, -CH-), 0.99 (6 H, d, J = 7 Hz, 2 -CH_3); δ_C (Me_2SO-d_6) 166.4 (C=O), 139.6, 135.1, 130.3, 128.7, 127.6, 127.0, 125.4, 55.7 (-CH-NH), 36.8, 31.9, 19.2, 18.3.

N-[(α-Phenyl)-1-butyl]benzamide (**2.8.1.2**)

Prepared (92%) from (**2.3.1.3**) using phenylmagnesium bromide, as a solid, m.p. 124-125°C (needles from 85% ethanol) (Found: C, 80.3; H, 7.7; N, 5.8. $C_{17}H_{19}NO$ requires: C, 80.6; H, 7.6; N, 5.5%); ν_{max} (KBr) 3230m, 1640s cm^{-1}; δ_H (Me_2SO-d_6) 8.52 (1 H, d, J = 8 Hz, NH), 7.89 (2 H, d, J = 7 Hz, H-2,6 of the benzamide ring), 7.55-7.17 (8 H, m, other aromatic protons), 5.89 (1 H, m, -CH-NH), 1.91-1.71 (2 H, m, -CH_2-), 1.46-1.08 (2 H, m, -CH_2-), 0.98-0.83 (3 H, m, -CH_3); δ_C (Me_2SO-d_6) 165.5 (C=O), 144.2, 134.3, 131.2, 131.0, 128.2, 127.3, 126.5, 126.4, 56.8 (-CH-NH), 38.0, 19.4, 13.6.

N[(α-Benzyl)-1-nonyl]benzamide (**2.8.1.3**)

Prepared (91%) from (**2.3.1.5**) using benzylmagnesium chloride, as a solid, m.p. 117-119°C {lit. m. p. 117-118.5°C (needles from ethanol) [66USP3256245]}; ν_{max} (nujol) 3280m, 1630s cm^{-1}; δ_H ($CDCl_3$) 7.71-7.76 (2 H, m, H-2,6 of the benzamide ring), 7.45-7.17 (8 H, m, other aromatic protons), 6.10 (1 H, d, J = 10 Hz, NH), 4.37 (1 H, m, -CH-NH), 2.89 (2 H, d, J = 6 Hz, -CH_2-Ph), 1.40-1.23 (14 H, m, other methylene protons), 0.89-0.87 (3 H, m, -CH_3); δ_C ($CDCl_3$) 167.0 (C=O), 138.0, 134.9, 131.1, 129.5, 128.4, 128.3, 126.8, 126.3, 50.5 (-CH-NH), 40.7, 34.0, 31.7, 29.4, 29.1, 26.1, 22.6, ,14.0.

N-[(α-Phenyl)-1-pentyl]benzamide (**2.8.1.4**)

Prepared (85%) from (**2.3.1.6**) using n-butylmagnesium bromide, as a solid, m.p. 129-130°C (needles from 85% ethanol) (Found: C, 80.6; H, 8.1; N, 5.3. $C_{18}H_{21}NO$ requires: C, 80.9; H, 7.9; N, 5.2%); ν_{max} (nujol) 3260w, 1620s cm^{-1}; δ_H (Me_2SO-d_6) 8.76 (1 H, d, J = 8 Hz, NH), 7.91 (2 H, d, J = 6 Hz, H-2,6 of the benzamide ring), 7.56-7.17 (8 H, m, other aromatic protons), 5.03 (1 H, q, J = 5 Hz, -CH-NH), 1.93-1.74 (2 H, m, -CH_2-), 1.34-1.24 (4 H, m, 2 -CH_2-), 0,89-0.83 (3 H, m, -CH_3); δ_C (Me_2SO-d_6) 165.8 (C=O), 144.2, 134.6, 131.0, 128.2, 128.1, 127.3, 126.5, 126.4, 53.2 (-CH-NH), 35.6, 28.5, 21.9, 13.8.

N-[(α-Phenyl)-4-methylphenyl]acetamide (**2.8.2.1**)

Prepared (93%) from (**2.3.2.3**) using phenylmagnesium bromide, as a solid, m.p. 124-125°C (needles from EtOAc/Pet.ether) (Found: C, 80.3; H, 7.2; N, 5.9. $C_{16}H_{17}NO$ requires: C, 80.3; H, 7.2; N, 5.7%); ν_{max} (KBr) 3300s, 1645s cm^{-1}; δ_H (Me_2SO-d_6) 8.78 (1 H, d, J = 8 Hz, NH), 7.29 (5 H, m, phenyl ring protons), 7.18 (4 H, m, other aromatic ring protons), 6.12 (1 H, d, J = 8 Hz, -CH-NH), 2,28 (3 H, s, CO-CH_3), 1.98 (3 H, s, -CH_3); δ_C (Me_2SO-d_6) 168.3 (C=O), 142.8, 139.6, 135.9, 128.8, 128.2, 127.2, 126.7, 55.5 (-CH-NH), 22.5, 20.5.

Reaction with Lithium Phenylacetylide

To the solution of phenylacetylene (1.02 g, 10 mmol) in 25 ml of tetrahydrofuran n-butyllithium (4.4 ml, 11 mmol, 2.5 M solution in hexanes) was added dropwise at -78°C under an argon atmosphere. Then the mixture was warmed up to room temperature and stirred for two hours to complete lithiation. Then the solution was cooled to 0°C and the benzotriazole adduct (5 mmol) in 20 ml of THF was added over a period of 15 minutes. The reaction mixture was stirred for additional 2 hours and then quenched with a few drops of water. The solvent was removed at 25°C/30 mmHg and the residue was extracted with ether (3 x 15 ml). The organic layer was washed with 2N NaOH (2 x 10 ml), water (2 x 15 ml) and dried with Na_2SO_4. Evaporation of the solvent gave a crude product which was purified by column chromatography using chloroform.

N-[1-(α-Phenylacetylenyl)-2-methylpropyl]benzamide (**2.9.1.1**)

Prepared (81%) from (**2.3.1.2**) as a solid, m.p. 94-95°C (needles from EtOAc/Pet.ether) (Found: C, 82.5; H, 7.2; N, 6.9. $C_{19}H_{19}NO$ requires: C, 82.3; H, 6.9; N, 5.1%); ν_{max} ($CHBr_3$) 3440w, 2250w, 1660s cm^{-1}; δ_H ($CDCl_3$) 7.81 (2 H, d, J = 7 Hz, H-2,6 of the benzamide ring), 7.45-7.29 (8 H, m, other aromatic protons), 6.48 (1 H, d, J = 8 Hz, NH), 5.11 (1 H, q, J = 8 Hz, -CH-NH), 2.15 (1 H, m, -CH-), 1.10 (6 H, d, J = 6 Hz, 2

-C<u>H</u>$_3$); δ_C ($CDCl_3$) 167.1 (C=O), 134.9, 132.4, 132.2, 129.2, 128.9, 127.6, 123.3, 87.6 (Ph-<u>C</u>), 84.7 (<u>C</u>-CH-), 48.9 (-<u>C</u>H-NH), 33.9, 19.7, 18.4.

<u>N-[1-(α-Phenylacetylenyl)-1-butyl]benzamide (**2.9.1.2**)</u>

Prepared (86%) from (**2.3.1.3**), as a solid, m.p. 84-85°C (needles from 85% ethanol) (Found: C, 82.0; H, 7.2; N, 5.1. $C_{19}H_{19}NO$ requires: C, 82.3; H, 6.9; N, 4.7%); ν_{max} ($CHBr_3$) 3420w, 2240w, 1650s cm^{-1}; δ_H ($CDCl_3$) 7.82 (2 H, d, J = 7 Hz, H-2,6 of the benzamide ring), 7.46-7.27 (8 H, m, other aromatic protons), 6.64 (1 H, d, J = 8 Hz, N<u>H</u>), 5.21 (1 H, m, -C<u>H</u>-NH), 1.82 (2 H, m, -C<u>H</u>$_2$-), 1.58 (2 H, m, -C<u>H</u>$_2$-), 0.98 (3 H, t, J = 8 Hz, -C<u>H</u>$_3$); δ_C ($CDCl_3$) 166.4 (C=O), 134.2, 131.7, 131.5, 128.5, 128.2, 127.3, 127.0, 122.7, 88.5 (Ph-<u>C</u>), 83.2 (<u>C</u>-CH), 42.3 (-<u>C</u>H-NH), 38.2. 19.1, 13.6.

CHAPTER III
N-MONOALKYLATION OF PRIMARY THIOAMIDES USING BENZOTRIAZOLE

3.1 Introduction

3.1.1 The Importance and Applications of Thioamides

The chemistry of thioamides has been developing rapidly during recent years. Thioamides have found wide technical application as, for example, metal deactivators in petrochemistry [66AG(E)(5)447], and (as described in the patent literature) vulcanization promoters, antioxidants, and corrosion inhibitors [56USP2688014, 59USP2875202, 62USP3035029]. Thioamides have been used as herbicides [63BEP612252, 64BEP626788, 65BEP639645]. Chlorothiobenzamides, cyclopropane, and cyclobutane derivatives have all shown herbicidal activity [70MI442].

Thioamides are important as pharmacologically active substances [50ZN79, 56CR2409, 59JGU(29)1106, 61N(47)450]. It is well known that thioacetamide possesses marked physiological activity. Thioacetamide can cause liver damage [61MI956]. α-Phenyl-α-(2-pyridyl)thioacetamide (antigastrin) (Figure 3.1) has anti-ulcer

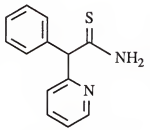


Figure 3.1

properties [65BEP669165, 67MI1240, 68MI81]. Some thiobenzamide derivatives (Figure 3.2) are strong antidiabetics [68MIP6706091]. 2-Ethylthioisonicotinamide shows significant ***in vivo*** activity toward *M. tuberculosis* and, because of its low toxicity,

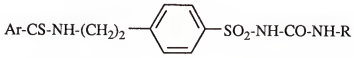


Figure 3.2

can be used as a human medicament [54JOC(19)753, 55JA(77)4062, 62MI46]. Activity of thioamides against other bacteria has been found by Weuffen and coworkers [66MI477], a substituted thiobenzamide (Figure 3.3) being especially effective. Salicylic acid thioanilide has fungistatic activity [66MI613].

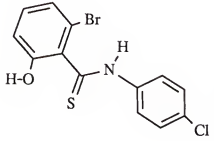
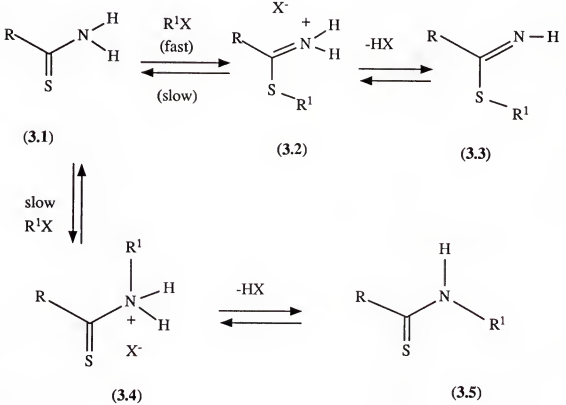


Figure 3.3

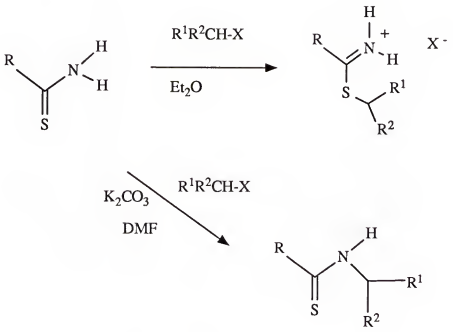
3.1.2 Review of the Methods Available in the Literature for Preparation of N-Alkylated Thioamides

No generally applicable method has been available for N-alkylation of thioamides. Thioamides possess two possible sites for alkylation: sulfur and nitrogen. Indeed, protonation of thioamides occurs on the sulfur atom to form sulphonium cations [61SA(17)530, 62RTC(81)65, 63CJC(41)2642] rather than on the nitrogen to form the corresponding ammonium ions [59SA(15)95]. Alkyl halides and other alkylating agents, as is well documented [70MI442, 79TL4671, 83SC757], react at the sulfur atom of thioamides (**3.1**) to yield S-alkylthioimidolium salts (**3.2**) which can be deprotonated



Scheme 3.1

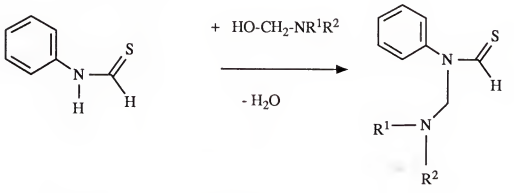
to form thioimidates (**3.3**) [80CB(113)171] (Scheme 3.1). Only from a limited range of alkylating agents, that form stable carbocations, such as triphenylmethyl chloride or xanthydryl alcohol, can the products (**3.5**) of N-alkylation be obtained [70MI442]. It was pointed out by Hurd [69JOC(34)269] that this type of N-alkylation is a result of the reversibility of the reaction (**3.1**) ⇌ (**3.2**). In such cases, gradual reaction *via* intermediate (**3.4**) can then proceed to the thermodynamically more stable product (**3.5**). This interpretation was supported by further work of Walter and Krohn [69CB(102)3786]. Alkylation of thioamides on nitrogen or sulfur was found to depend upon the reaction conditions. Using bis(p-methoxyphenyl)methyl chloride for the alkylation of thioacetamide and thiobenzamide led to thiolimidate ester hydrochlorides, whereas, in the presence of potassium carbonate as a base, N-alkylated products were obtained (Scheme 3.2).



Scheme 3.2

The authors also reported alkylation using substituted benzhydryl carbinols in acidic media and the thermal rearrangement of the thiolimidate esters into the thermodynamically more favored N-alkylated thioamide isomer.

Mohrle and Spillman [72T(28)199] have investigated the behavior of thioamides under Mannich reaction conditions (Scheme 3.3) and found that a successful N-aminomethylation is drastically dependent on steric requirements. The preparation of Mannich bases with monosubstituted thioformamides has been described. Attempts to apply that procedure to thioamides other than thioformamides failed.



Scheme 3.3

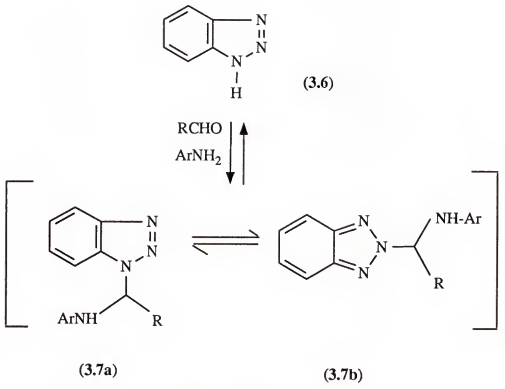
Recently, other examples of aminomethylation of pyridine and pyrazine carboxythioamides have been reported [73MI109, 129]. The hydroxyalkylation and alkoxyalkylation of thioamides have been found to give N-substituted products [74AP(307)748, 77AP(310)442, 996, 77AP(310)1001, 77S250].

Some other alkylating agents, such as diazomethane under neutral conditions on silica gel [79TL4671], or ethyl thiochloroformate [73JOC(38)2242], have been exploited recently for the alkylation of thioamides. These reagents also led to S-alkylation products. Thiocaprolactams, thiobenzamide, thioacetanilide and thioisonicotinamide were easily

methylated with diazomethane to afford the corresponding thioimidates in high yields. A review of the literature published up to this date showed that no generally applicable method is available for the N-monoalkylation of thioamides.

3.1.3 Aim of the Work

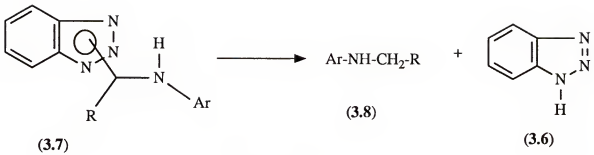
The purpose of the present work was to develop a general synthetic procedure applicable to all types of thioamides, that would lead exclusively to the products of alkylation on the nitrogen. Results previously obtained by Katritzky and coworkers have shown that the readily available products (**3.7**) from aminoalkylation of benzotriazole (**3.6**) (Scheme 3.4) were reduced with sodium borohydride in high yield to N-alkylaryl-amines (**3.8**) (Scheme 3.5).



(**3.6**)

(**3.7a**) (**3.7b**)

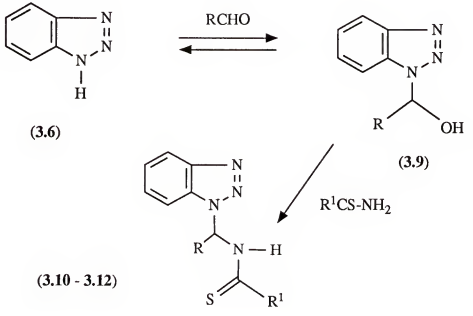
Scheme 3.4



Scheme 3.5

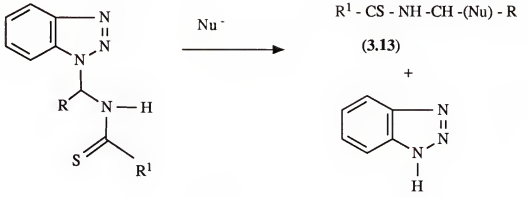
It was even possible to N-alkylate heteroarylamines such as 2-aminopyridine and adenine [87JCS(P1)799,805]. Lately this method has been extended to aliphatic secondary amines [88JCS(P1)IP1] and amides (see Chapter II).

Formation of adducts (**3.10**-**3.12**) from thioamides, aldehydes, and benzotriazole (Scheme 3.6) should proceed with formation of the intermediate 1-(hydroxyalkyl)benzo-



Scheme 3.6

triazole (**3.9**). Subsequent cleavage of benzotriazole by an incoming nucleophile should be a further extension of this work and provide, for the first time, a general and regio-selective (only on nitrogen atom) method for the preparation of secondary thioamides (Scheme 3.7).



Scheme 3.7

3.2 Results and Discussion

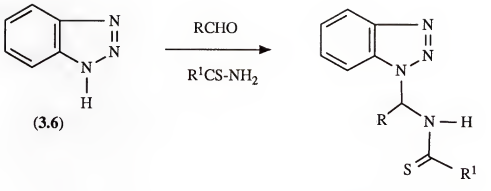
3.2.1 Formation of Adducts (**3.10-3.12**)

Various aliphatic aldehydes were treated with thiobenzamide, thiourea, and thioisonicotinamide in the presence of benzotriazole. Heating these mixtures in toluene (Table 3.1) led to the formation of adducts (**3.10-3.12**) and an almost quantitative amount of water (Scheme 3.8). The latter was removed azeotropically using a Dean-Stark adapter.

Table 3.1 Preparation of N-[1-(Benzotriazol-1-yl)alkyl]thioamides (**3.10**)-(**3.12**)

Product	R of RCHO	$R^1$of R^1CSNH_2	Time (h)	Yield (%)	Recryst. solvent	M.p. (°C)
(**3.10.1**)	H	Ph	9	53	Benzene/EtOH	203-206
(**3.10.2**)	Pr^i	Ph	48	48	Benzene	193-195
(**3.10.3**)	Pr^n	Ph	27	71	Benzene	160-164
(**3.10.4**)	$Pent^n$	Ph	6	44	Benzene	145-148
(**3.10.5**)	$Heptyl^n$	Ph	9	62	Ethanol	134-136
(**3.10.6**)	$Octyl^n$	Ph	5	67	Benzene	138-143
(**3.10.7**)	$Undecyl^n$	Ph	24	45	Ethanol	117-120
(**3.11.1**)	Pr^i	NH_2	48	46	Acetone	199-200
(**3.11.2**)	$Heptyl^n$	NH_2	20	35	Acetone	178-180
(**3.12.1**)	$Pentyl^n$	4-Py	6	48	-	Oil
(**3.12.2**)	$Heptyl^n$	4-Py	24	85	-	Oil
(**3.12.3**)	$Nonyl^n$	4-Py	24	75	-	Oil

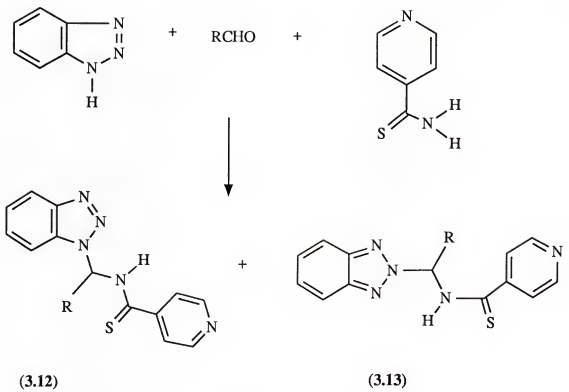
This procedure was successful for aliphatic aldehydes on the 0.1 molar scale. All crude materials were purified by recrystallization from the appropriate solvents. The adducts derived from thiobenzamide and thiourea (**3.10**-**3.11**) were solids. All products were characterized by their spectral and analytical properties (see Experimental for details).



(**3.10**) R^1 = Ph
(**3.11**) R^1 = NH_2
(**3.12**) R^1 = 4-Pyridyl

Scheme 3.8

It is known from earlier work by Katritzky *et al.* [87JCS(P1)2673], that aminoaryl derivatives of benzotriazole (**3.7**) exist in solution as a mixture of rapidly interconverting 1- and 2-isomers (**3.7a**) and (**3.7b**) (Scheme 3.4) with the 1-substituted compound (**3.7a**) predominanting. In the case of amide adducts (see Chapter II), only one isomer was obtained. Preparation of thioamide adducts yielded only one isomer when thiobenzamide or thiourea were used. However, two isomers were observed when isothionicotinamide was used (Scheme 3.9). Adducts (**3.12**) **and** (**3.13**) were successfully separated by column chromatography on silica gel and fully characterized by their spectral data (Table 3.2). The structures of the corresponding 1-isomers (**3.12.1**)-(**3.12.3**) were supported by their elemental analyses. All derivatives of thioisonicotinamide were oils. Attempted distillation and prolonged storage of (**3.12**) and (**3.13**) led to decomposition.



(3.12) **(3.13)**

Scheme 3.9

The chemical shifts of the benzotriazole carbons in 1-substituted adducts **(3.10)**-**(3.12)** corresponded to values previously reported [83H(20)1787]. The quaternary carbons C-3a and C-7a appeared at δ 145.1-144.2 ppm and δ 133.2-131.4 ppm respectively. The chemical shift for the thiocarbonyl carbon was downfield at δ 183 ppm for the thiourea and δ 201.1-198.0 ppm for the other thioamides. The adducts **(3.13)** in which the alkylthioamide group was bonded to the N-2 of the benzotriazole moiety had a symmetrically substituted benzotriazole nucleus. These adducts displayed only three peaks for C-3a, C-4, and C-5 at δ 144.1-143.9 ppm, δ 118.9-118.2 ppm, and δ 127.0-126.7 ppm respectively. These chemical shifts were in good agreement with values reported for 2-substituted isomers of benzotriazole [83H(20)1787].

Table 3.2 ^{13}C NMR Chemical Shifts for Thiocarbonyl, Benzotriazole, and C-α Carbons in Compounds (**3.10**)-(**3.13**)

Product	C=S	C-3a	C-4	C-5	C-6	C-7	C-7a	CH-NH-
(3.10.1)	199.6	144.3	118.0	122.9	126.7	109.9	131.4	55.5
(3.10.2)	201.1	144.7	119.2	124.0	127.4	111.2	132.9	73.8
(3.10.3)	199.9	144.2	118.2	122.9	126.5	109.9	131.6	67.1
(3.10.4)	200.4	145.1	119.3	124.4	127.8	110.6	133.2	67.5
(3.10.5)	200.5	145.0	119.0	124.1	127.5	111.0	132.3	68.6
(3.10.6)	200.4	145.1	119.3	124.4	127.1	110.6	133.2	67.6
(3.10.7)	200.4	145.2	119.5	124.4	127.1	110.6	133.2	67.5
(3.11.1)	183.8	144.7	118.9	123.8	127.1	111.2	132.8	73.0
(3.11.2)	183.6	145.0	119.1	124.0	127.2	110.8	132.3	67.3
(3.12.1)	198.1	145.0	119.3	124.6	128.0	110.5	133.2	67.5
(3.12.2)	198.0	144.9	119.1	124.4	127.8	110.4	133.1	67.5
(3.12.3)	198.1	145.0	119.3	124.6	128.0	110.5	133.1	67.5
(3.13.1)	197.6	144.1	118.4	127.0	127.0	118.4	144.1	74.5
(3.13.2)	197.9	143.9	118.2	126.8	126.8	118.2	143.9	74.5
(3.13.3)	197.9	143.9	118.9	126.7	126.7	118.9	143.9	74.5

In addition, the ^{13}C NMR spectra of the products (**3.10**) showed four signals corresponding to the thiobenzamide carbons. A comparison of chemical shifts with the unsubstituted thiobenzamide showed only a small substituent effect. Adducts (**3.12**) and

(**3.13**) showed the characteristic peaks for three carbon types in the pyridine ring (Table 3.3). The aliphatic carbons in the R substituents of all adducts displayed patterns similar to the amide adducts (see Chapter II).

Table 3.3 ^{13}C NMR Chemical Shifts of the Carbons in R^1 Substituents in Products (**3.12**), and (**3.13**)

Compound	C-ipso	C-2'	C-3'
(**3.12.1**)	147.7	121.2	149.5
(**3.12.2**)	147.7	121.2	149.1
(**3.12.3**)	147.6	121.2	149.5
(**3.13.1**)	147.7	120.6	150.2
(**3.13.2**)	148.1	121.1	149.3
(**3.13.3**)	148.1	121.1	149.2

In the ^1H NMR spectra of all the thioamide-alkyl adducts of benzotriazole (**3.10.4**)-(**3.10.7**), the most deshielded proton appeared in the region δ 11.32-9.10 ppm. This peak usually appeared as a doublet with a coupling constant in the range of 6 to 8 Hz. This doublet has been assigned to the NH proton of the thioamide group. The proton attached to C-α (Figure 3.4) was deshielded by the two nitrogens and often could not be distinguished from the aromatic protons. The attached β-methylene protons gave rise to a complex multiplex in the region δ 2.63-2.02 ppm. The other aliphatic protons were usually not assigned because of the complexity of their signals. The methyl groups of

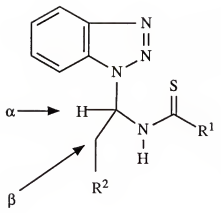


Figure 3.4

the isopropyl substituent in (**3.10.2**) (Figure 3.5) were not equivalent and appeared as well resolved doublets at δ 1.30 ppm and δ 0.71 ppm with a coupling constant of 7 Hz.

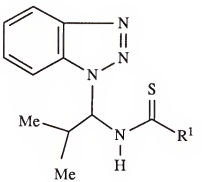
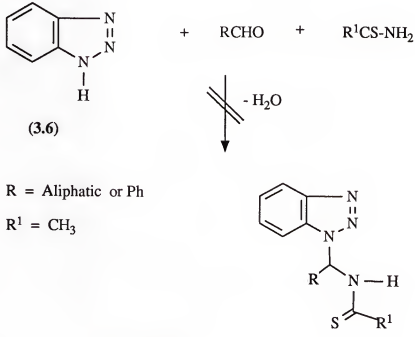


Figure 3.5

An examination of the infrared spectra of the products allowed easy identification of the absorption peaks corresponding to the NH stretching vibration 3240-3150 cm^{-1} and the moderate intensity thiocarbonyl band near 1500 cm^{-1}.

3.2.2 Attempts at the Reaction of Benzotriazole with Aliphatic Thioamides and Aldehydes

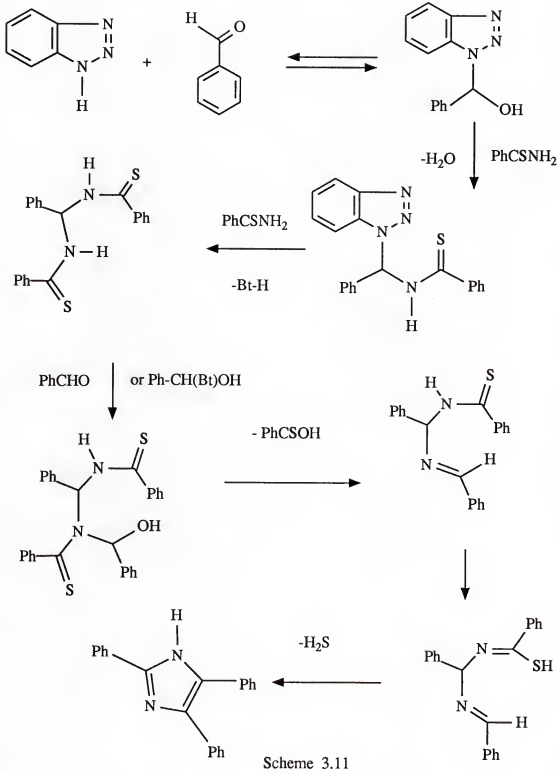
The primary aliphatic thioamides were unreactive toward benzotriazole and aliphatic or aromatic aldehydes in refluxing toluene. Only starting materials and some polymeric products with a horrible odor were recovered. Use of p-toluenesulfonic acid as a catalyst did not yield the desired product (Scheme 3.10).



Scheme 3.10

3.2.3 Reaction of Benzotriazole with Benzaldehyde and Thiobenzamide

Refluxing an aromatic aldehyde, thiobenzamide and benzotriazole in a 1:1:1 ratio led to a completely unexpected product. From the analytical and spectral data available for this compound, it was concluded that the product was 2,4,5-triphenyl-1*H*-imidazole. A possible mechanistic pathway is given in Scheme 3.11.

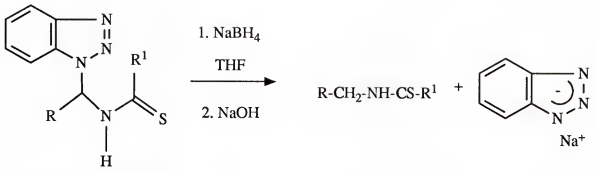


Scheme 3.11

Analysis for C, H, and N agreed with that calculated for $C_{21}H_{16}N_2$ within 0.2%. The IR spectrum of the product showed an absorption at 2800-2900 cm^{-1} that could be attributed to NH stretching vibrations. The ^{13}C NMR spectrum displayed two distinguishable quaternary carbons. The chemical shift at δ 145.6 ppm was assigned to C-2 of the imidazole ring and the δ 130.4 ppm shift to both C-4 and C-5 of the imidazole. The remaining peaks corresponded to the carbons of the phenyl substituents. The ^1H NMR spectrum exhobit a distinct doublet at δ 8.13 ppm with a coupling constant of 8 Hz (corresponding to two hydrogens) followed by multiplet at δ 7.58-7.72 ppm of 13 protons. There was a broad signal at about δ 3.4 ppm due to the NH proton. The proposed structure of the product was supported by its melting point 273-275°C (literature melting point for 2,4,5-triphenyl-1*H*-triazole is 273°C [82ZOU(18)2273]. Comparison with an authentic sample (Aldrich) by thin layer chromatography, mixed melting point, and mass spectroscopic evidence verified the identity of the compound.

3.2.4 Reduction of N-[1-(Benzotriazol-1-yl)alkyl]thioamides with Sodium Borohydride

The adducts (**3.10**) and (**3.11**) were completely reduced with sodium borohydride in refluxing tetrahydrofuran in 30 minutes. Benzotriazole, as its sodium salt, was removed during the basic workup and the N-alkylated thiobenzamide was isolated in excellent yield (Scheme 3.12). N-Monoalkylated thioureas gave lower yields. The products (**3.14**) and (**3.15**) were pure by ^1H NMR and TLC. The experimental results are given in the Table 3.4.



(3.10) $R^1 = Ph$ **(3.14)** $R^1 = Ph$

(3.11) $R^1 = NH_2$ **(3.15)** $R^1 = NH_2$

Scheme 3.12

All the synthesized products were characterized by their ^1H, ^{13}C, and IR spectral properties. The most indicative peaks in the ^{13}C NMR spectra were the chemical shifts of the thiocarbonyl carbon that appeared in the region δ 199.4-197.3 ppm for the thiobenzamide and δ 183.3-181.3 ppm for thiourea derivatives. The methylene carbon C-α attached to the thioamide nitrogen was downfield and appeared at δ 53.4-44.4 ppm. The ipso-carbon and C-4 of the thiobenzamide in compounds (**3.14**) were easily identified at δ 141.7-140.9 ppm and δ 130.9-130.4 ppm respectively. The chemical shifts of C-2 and C-3 were interchangeable. In the ^1H NMR spectra of the secondary thioamides, the most deshielded peak was assigned to the NH proton. This peak usually appeared as a broad signal. Characteristic IR frequencies were found for NH stretching vibrations, usually as

strong absorption in the region 3250-3220 cm^{-1}, and a thiocarbonyl band of strong to moderate intensity around 1500 cm^{-1}.

Table 3.4 Preparation of N-Alkylthioamides (**3.14**) and Thioureas (**3.15**)

Product	R of RCHO	R^1 of R^1CSNH_2	Yield (%)	Phys. form	M.p. (°C)	Lit.M.p. (°C)
(3.14.1)	H	Ph	98	Microcr.	77-80	79-80[a]
(3.14.2)	Pr^i	Ph	99	Oil[b]	-	-
(3.14.3)	$Pent^n$	Ph	92	Oil[c]	-	-
(3.14.4)	$Heptyl^n$	Ph	95	Oil[d]	-	-
(3.14.5)	$Octyl^n$	Ph	97	Oil[e]	-	-
(3.15.1)	Pr^i	NH_2	60	Prisms	99-101	100-101[f]
(3.15.2)	$Heptyl^n$	NH_2	60	Plates	98	96-98[g]

[a][76ACS(B)837] [b]MS: for $C_{11}H_{15}NS$ calc. 193.0925, found 193.0922 [c]MS: for $C_{13}H_{19}NS$ calc. 221.1238, found 221.1235 [d]B.p.194-198°C/2 mmHg, lit. b.p.196-197°C/2 mmHg [70MI1980] [e]MS: for $C_{16}H_{25}NS$ calc. 263.1707, found 263.1677 [f][53ACS(2)528] [g][61JAP13624].

3.2.5 Reaction of Adducts (**3.10**) with Grignard Reagents

Preparation of substituted thioamides could be achieved by alternative approaches in which bonds a, b, or c are constructed (Figure 3.6) as the key step. Formation of bond (a) could be accomplished using organometallic compounds as nucleophiles and isothio-

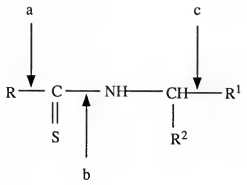
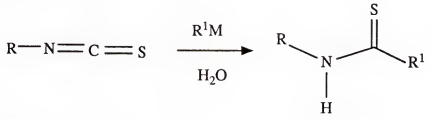


Figure 3.6

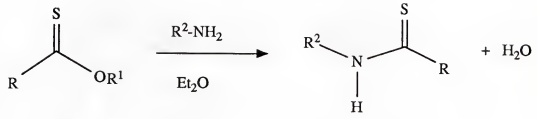
cyanates as electrophiles. Addition of organomagnesium or organolithium reagents to isothiocyanates resulted, after hydrolysis, in the formation of N-substituted thioamides [50JA(72)1661, 73S678] (Scheme 3.13).



R^1 = Mg, Li

Scheme 3.13

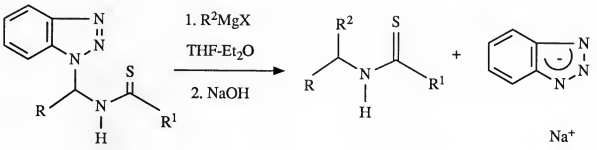
Formation of the bond (b) resulted when an amine was used as a nucleopile and a thiocarboxylic acid, chloride, or ester as an electrophile [65BSF3623] (Scheme 3.14).



Scheme 3.14

Bond (c) could be constructed by deprotonation of the methylene carbon followed by alkylation (as was described for amides in the Chapter II). Alternatively, the strategy developed for amides could be extended to thioamides. Nucleophilic substitution at the carbon alpha to the thioamide nitrogen has not been previously reported in the literature.

Reaction of 2.1 equivalents of a Grignard reagent with N-[1-(benzotriazol-1-yl)-alkyl]thioamides **(3.10)** (Scheme 3.15) in a mixture of THF and diethyl ether gave



(3.10) **(3.16)**

Scheme 3.15

secondary thioamides in good yields. Benzotriazole was removed from the reaction mixture by alkaline extraction. All secondary thioamides were purified by column chromatography using silica gel. High resolution mass spectra allowed for accurate determination of the molecular formula for all synthesized products (Table 3.5).

Table 3.5 Preparation of Secondary Thioamides (**3.16**) $RR^2CH\text{-}NH\text{-}CS\text{-}R^1$ (R^1 = Ph)

Product	R	$R^2$of R^2MgX	Yield (%)	Molec. formula	Found	Calculated
(3.16.1)	H	$PhCH_2$	84	$C_{15}H_{15}NS$	241.0919	241.0925
(3.16.2)	Pr^i	$PhCH_2$	87	$C_{18}H_{21}NS$	283.1393	283.1394
(3.16.3)	Pr^n	Bu^n	89	$C_{15}H_{23}NS$	249.1546	249.1551
(3.16.4)	$Pent^n$	Ph	88	$C_{19}H_{23}NS$	297.1537	297.1551
(3.16.5)	$Undecyl^n$	$PhCH_2$	81	$C_{26}H_{37}NS$	395.2633	395.2646

All thioamides were characterized by their spectral properties. In their IR spectra, characteristic absorptions were observed for NH stretching vibrations in the region of 3380-3240 cm^{-1} and for the thiocarbonyl group at 1520-1508 cm^{-1}. In the ^{13}C NMR spectra the thiocarbonyl carbon chemical shift was downfield at δ 199.1-196.3 ppm. The signal for the methine carbon attached to the nitrogen appeared at δ 61.3-47.4 ppm. The positions of the remaining carbons were similar to those of the parent adducts.

3.3 Conclusions

The unique method presented above offers a procedure for preparation of N-alkylated thioamides. This two-step sequence proceeds in good overall yields, uses readily available reagents, and can be performed on a large scale. Although this procedure cannot be applied to aliphatic thioamides, it does offer generality with respect to the introduced alkyl group. The conditions for this reaction are relatively mild, there is no possibility of introducing more than one alkyl group, and the reaction occurs regioselectively at the nitrogen atom.

3.4 Experimental

The apparatus and general procedures used in this Chapter are identical to those described in Chapter II. Additionally, ^{1}H NMR spectra were run, where specified, on a Varian XL300 (300 MHz, FT mode). Mass spectra were obtained at 70 eV on an AEI MS 30 spectrometer operating with DS-55 data system. Column chromatographies were carried out using MCB silica gel (230-400 Mesh).

3.4.1 General Procedure for Preparation of N-[1-(Benzotriazol-1-yl)alkyl]thioamides (**3.10**)-(**3.12**)

Method A

N-Hydroxymethylbenzotriazole (14.9 g, 0.1 mol), the thioamide (0.1 mol), and 40 ml of dry toluene were refluxed in a Dean-Stark apparatus for the appropriate length of time and the collected water was removed. Toluene was removed at 60°C/30 mmHg. The residue was treated with 200 ml of diethyl ether and the resulting solid recrystallized from the appropriate solvent to give adducts (**3.10**)-(**3.12**).

Method B

Benzotriazole (11.9 g, 0.1 mol), an aldehyde (0.1 mol) and a thioamide (0.1 mol) were refluxed for 5-48 hours in 40 ml of dry toluene in a Dean-Stark apparatus. Water collected (about 1.5 ml) was removed. Toluene was removed on a rotary evaporator (60°C/30 mmHg) and the residue was treated with 200 ml of diethyl ether. The crude product was recrystallized from the appropriate solvent or purified by column chromatography.

N-[1-(Benzotriazol-1-yl)methyl]thiobenzamide (**3.10.1**)

Prepared (53%) from N-hydroxymethylbenzotriazole and thiobenzamide after 9 hours, as a solid, m.p. 203-206°C (needles from benzene/ethanol 1:4) (Found: C, 62.7; H, 4.4; N, 21.0. $C_{14}H_{12}N_4S$ requires: C, 62.5; H, 4.5; N, 20.9%); ν_{max} (nujol) 3240w, 1540m, 1150m cm^{-1}; δ_H (Me_2SO-d_6) 11.14 (1 H, broad, NH), 8.04 (1 H, d, J = 8 Hz, H-4), 7.98 (1 H, d, J = 8 Hz, H-7). 7.89 (2 H, d, J = 7 Hz, H-5,6), 7.54-7.29 (5 H, m, phenyl ring protons), 6.68 (2 H, s, -CH_2-NH); δ_C (Me_2SO-d_6) 199.6 (C=S), 144.3, 139.3, 131.4, 130.0, 126.7, 126.3, 122.9, 118.0, 109.9, 55.5 (-CH_2-NH).

N-[1-(Benzotriazol-1-yl)-2-methylpropyl]thiobenzamide (**3.10.2**)

Prepared (48%) from benzotriazole, isobutyraldehyde, and thiobenzamide after 48 hours as a solid, m.p. 193-195°C (needles from benzene) (Found: C, 65.8; H, 5.8; N, 18.0. $C_{17}H_{18}N_4S$ requires: C, 65.8; H, 5.8; N, 18.0%); ν_{max} (nujol) 3190m, 1535m, 1155m cm^{-1}; δ_H (Me_2SO-d_6) 11.28 (1 H, d, J = 8 Hz, NH), 8.09 (1 H, d, J = 8 Hz, H-4), 7.98 (1 H, d J = 8 Hz, H-7), 7.73 (2 H, d, J = 8 Hz, H-5,6), 7.53-7.31 (5 H, m, protons of the phenyl ring), 7.15 (1 H, t J = 9 Hz, -CH-NH), 3.35-3.06 (1 H, m, -CH-), 1.30 (3 H, d, J = 7 Hz, -CH_3), 0.71 (3 H, d, J = 7 Hz, -CH_3); δ_C (Me_2SO-d_6) 201.1 (C=S), 144.7, 140.8, 132.9, 131.1, 127.9, 127.5, 127.4, 124.0, 119.2, 111.2, 73.8 (CH-NH), 31.9, 18.9, 18.1.

N-[1-(Benzotriazol-1-yl)butyl]thiobenzamide (**3.10.3**)

Prepared (71%) from benzotriazole, butyraldehyde, and thiobenzamide after 27 hours as a solid, m.p. 160-164°C (prisms from benzene) (Found: C, 65.8; H, 5.8; N, 17.7. $C_{17}H_{18}N_4S$ requires: C, 65.8; H, 5.8; N, 18.0%); ν_{max} (nujol) 3180m, 1510s, 1140m cm^{-1}; δ_H ($CDCl_3$) 11.11 (1 H, d, J = 8 Hz, NH), 8.07-8.00 (2 H, m, H-4,7), 7.76-7.72 (2 H, m, H-5,6), 7.56-7.28 (6 H, m, phenyl ring protons and -CH-NH), 2.63-2.51 (2 H, m, $-CH_2-$), 1.58-1.26 (2 H, m, $-CH_2-$), 0.99 (3 H, t, J = 7 Hz, $-CH_3$); δ_C ($CDCl_3$) 199.9 (C=S), 144.2, 139.9, 131.6, 129.9, 126.7, 126.6, 126.5, 126.3, 122.9, 118.2, 109.9, 67.1 (-CH-NH), 34.3, 17.4, 12.4.

N-[1-(Benzotriazol-1-yl)hexyl]thiobenzamide (**3.10.4**)

Prepared (44%) from benzotriazole, hexanal, and thiobenzamide after 6 hours, as a solid, m.p. 145-148°C (plates from benzene) (Found: C, 67.5; H, 6.7; N, 16.5. $C_{19}H_{22}N_4S$ requires: C, 67.4; H, 6.6; N, 16.8); ν_{max} (nujol) 3150m, 1545m, 1150w cm^{-1}; δ_H ($CDCl_3$) 9.38 (1 H, d, J = 8 Hz, NH), 7.97-7.25 (10 H, m, all aromatic protons and -CH-NH), 2.60-2.51 (2 H, m, $-CH_2-$), 1.43-1.15 (6 H, m, 3 $-CH_2-$), 0.86-0.77 (3 H, m, $-CH_3$); δ_C ($CDCl_3$) 200.4 (C=S), 145.1, 140.6, 133.2, 131.5, 128.2, 127.8, 124.4, 119.3, 110.6, 67.5 (-CH-NH), 34.1, 31.0, 24.7, 22.2, 13.8.

N-[1-(Benzotriazol-1-yl)octyl]thiobenzamide (**3.10.5**)

Prepared (62%) from benzotriazole, octanal, and thiobenzamide after 9 hours, as a solid m.p. 134-136°C (needles from ethanol) (Found: C, 68.8; H, 7.1; N, 15.1. $C_{21}H_{26}N_4S$ requires: C, 68.8; H, 7.2; N, 15.3%); ν_{max} (nujol) 3160w, 1580w, 1150w, cm^{-1}; δ_H (Me_2SO-d_6) 11.32 (1 H, d, J = 8 Hz, NH), 8.06-8.03 (2 H, m, H-4,7), 7.69 (2 H, d, J = 7 Hz, H-5,6), 7.59-7.39 (6 H, m, phenyl ring protons and -CH-NH), 2.51-2.46 (2 H, m, $-CH_2-$), 1.33-1.14 (10 H, m, methylene protons), 0.95-0.79 (3 H, m, $-CH_3$); δ_C

(Me_2SO-d_6) 200.5 (C=S), 145.0, 140.7, 132.3, 131.2, 127.9, 127.5, 127.4, 124.1, 119.0, 111.0, 68.6 (-CH-NH), 33.0, 31.0, 28.4, 28.3, 24.6, 22.0, 13.8.

N-[1-(Benzotriazol-1-yl)nonyl]thiobenzamide (**3.10.6**)

Prepared (67%) from benzotriazole, nonanal, and thiobenzamide after 5 hours, as a solid, m.p. 138-143°C (plates from benzene) (Found: C, 69.6; H, 7.4; N, 14.7. $C_{22}H_{28}N_4S$ requires: C, 69.4; H, 7.4; N, 14.7%); ν_{max} (nujol) 3170m, 1570w, 1155m cm^{-1}; δ_H ($CDCl_3$) 9.40 (1 H, d, J = 6 Hz, NH), 7.92 (2 H, m, H-4,7), 7.87-7.76 (2 H,m, H-5,6), 7.67-7.24 (6 H, m, phenyl ring protons and -CH-NH), 2.56 (2 H, m, -CH_2-), 1.32-1.15 (12 H, m, methylene protons), 0.87-0.81 (3 H, m, -CH_3); δ_C ($CDCl_3$) 200.4 (C=S), 145.1, 140.6, 133.2, 131.5, 128.2, 127.1, 124.4, 119.3, 110.6, 67.6 (-CH-NH), 34.1, 31.6, 29.1, 29.0, 28.8, 24.9, 22.5, 13.9.

N-[1-(Benzotriazol-1-yl)dodecyl]thiobenzamide (**3.10.7**)

Prepared ((45%) from benzotriazole, dodecanal, and thiobenzamide after 24 hours, as a solid, m.p. 117-120°C (microcrystals from ethanol) (Found: C, 71.1; H, 8.1. $C_{25}H_{34}N_4S$ requires: C, 71.1; H, 8.1%); ν_{max} (nujol) 3185s, 1590w, 1250w cm^{-1}; δ_H ($CDCl_3$) 9.10 (1 H, d, J = 8 Hz, NH), 7.93 (1 H, d, J = 8 Hz, H-4), 7.76 (1 H, d, J = 7 Hz, H-7), 7.74-7.27 (8 H, m, other aromatic protons and -CH-NH), 2.56 (2 H, m, -CH_2-), 1.32-1.21 (18 H, m, methylene protons), 0.87-0.83 (3 H, m, -CH_3); δ_C ($CDCl_3$) 200.4 (C=S), 145.2, 140.7, 133.2, 131.6, 128.4, 127.1, 124.4, 119.5, 110.6, 67.5 (-CH-NH), 34.4, 31.8, 29.5, 29.4, 29.2, 28.9, 25.0, 22.6, 14.0.

N-[1-(Benzotriazol-1-yl)-2-methylpropyl]thiourea (**3.11.1**)

Prepared (46%) from benzotriazole, isobutyraldehyde, and thiourea after 48 hours, as a solid, m.p. 199-200°C (needles from acetone) (Found: C, 53.0; H, 6.3; N, 28.2. $C_{11}H_{15}N_5S$ requires: C, 53.0; H, 6.1; N, 28.1%); ν_{max} (nujol) 3160w, 1160w cm^{-1}; δ_H (300 MHz) (Me_2SO-d_6) 9.17 (1 H, d, J = 9 Hz, NH), 8.22 (2 H, d, J = 9 Hz, H-4,7), 7.72 (1 H, t,

J = 8 Hz, H-5), 7.57 (1 H, t, J = 8 Hz, H-6), 7.08 (1 H, t, J = 9 Hz, -CH-NH), 3.40 (2 H, s, NH_2-), 2.84 (1 H, m, -CH-), 1.30 (3 H, d, J = 6.5 Hz, -CH_3), 0.86 (3 H, d, J = 6.5 Hz, -CH_3); δ_C (75 MHz) (Me_2SO-d_6) 183.8 (C=S), 144.7, 132.8, 127.1, 123.8, 118.9, 111.2, 73.0 (-CH-NH), 33.1, 18.6, 18.2.

N-[1-(Benzotriazol-1-yl)-1-octyl]thiourea (**3.11.2**)

Prepared (35%) from benzotriazole, octanal, and thiourea after 20 hours, as a solid, m.p. 178-180°C (needles from acetone) (Found: C, 59.4; H, 7.3; N, 22.9. $C_{15}H_{23}N_5S$ requires: C, 59.0; H, 7.6; N, 22.9%); ν_{max} (nujol) 3220w, 1160m cm^{-1} ; δ_H (Me_2SO-d_6) 8.98 (1 H, d, J = 8 Hz, NH), 8.44-7.85 (2 H, m, H-4,7), 7.57-7.11 (3 H, m, H-5,6, -CH-NH), 3.49 (2 H, s, NH_2), 2.25-2.18 (2 H, m, -CH_2), 1.18-0.98 (10 H, m, 3 -CH_2-), 0.80-0.73 (3 H, m, -CH_3); δ_C (Me_2SO-d_6) 183.6 (C=S), 145.0, 132.3, 127.2, 124.0, 119.1, 110.8, 67.3 (-CH-NH), 34.5, 31.0, 28.4, 28.2, 24.6, 22.0, 13.8.

N-[1-(Benzotriazol-1-yl)hexyl]thioisonicotinamide (**3.12.1**)

Prepared (48%) from benzotriazole, hexanal, and thioisonicotinamide after 6 hours, as an oil, purified by column chromatography on silica gel with chloroform (Found: C, 63.6; H, 6.3. $C_{18}H_{21}N_5S$ requires: C, 63.9; H, 6.2%); δ_H ($CDCl_3$) 10.88-10.82 (1 H, m, NH), 8.43-8.36 (2 H, m, H-2,6 of pyridine ring), 7.94-7.85 (2 H, m, H-4,7), 7.50-7.28 (5 H, m, other aromatic protons and -CH-NH), 2.57-2.02 (2 H, m, -CH_2-), 1.44-1.11 (6 H, m, methylene protons), 0.84-0.73 (3 H, m, -CH_3); δ_C ($CDCl_3$) 198.1 (C=S), 149.5, 147.7, 145.0, 133.2, 128.0, 124.6, 121.2, 119.3, 110.5, 67.5 (-CH-NH), 33.8, 30.9, 24.7, 22.2, 13.7.

N-[1-(Benzotriazol-1-yl)octyl]thioisonicotinamide (**3.12.2**)

Prepared (85%) from benzotriazole, octanal, and thioisonicotinamide after 24 hours, as an oil, purified by column chromatography on silica gel, using chloroform; (Found: C, 65.3; H, 6.9. $C_{20}H_{25}N_5S$ requires: C, 65.4; H, 6.9%); δ_H ($CDCl_3$) 11.28 (1 H,

d, J = 9 Hz, NH), 8.35 (2 H, d, J = 6 Hz, H-2,6 of pyridine ring), 7.97-7.89 (2 H, m, H-4,7), 7.62-7.49 (4 H, m, other aromatic protons), 7.40-7.32 (1 H, m, -CH-NH), 2.59 (2 H, m, $-CH_2-$), 2.11-1.08 (10 H, m, methylene protons), 0.84-0.76 (3 H, m, $-CH_3$); δ_C ($CDCl_3$) 198.0 (C=S), 149.1, 147.7, 144.9, 133.1, 127.8, 124.4, 121.2, 119.1, 110.4, 67.5 (-CH-NH), 33.6, 31.3, 28.6, 24.9, 22.2, 13.8.

N-[1-(Benzotriazol-1-yl)decyl]thioisonicotinamide (**3.12.3**)

Prepared (75%) from benzotriazole, decanal, and thioisonicotinamide after 24 hours, as an oil, purified by column chromatography on silica gel, using ethyl acetate - chloroform (1:1); (Found: C, 66.8; H, 7.4. $C_{22}H_{29}N_5S$ requires: C, 66.8; H, 7.4%); δ_H ($CDCl_3$) 10.82 (1 H, d, J = 9 Hz, NH), 8.44-8.39 (2 H, m, H-2,6 of the pyridine ring), 7.95-7.89 (2 H, m, H-4,7), 7.57-7.28 (5 H, m, other aromatic protons and -CH-NH), 2.56-2.51 (2 H, m, $-CH_2-$), 1.31-1.00 (14 H, m, other methylene protons), 0.88-0.77 (3 H, m, $-CH_3$); δ_C ($CDCl_3$) 198.1 (C=S), 149.5, 147.6, 145.0, 133.2, 128.0, 124.6, 121.2, 119.3, 110.5, 67.5 (-CH-NH), 33.8, 31.7, 29.3, 29.1, 29.05, 28.8, 25.05, 22.5, 14.0.

3.4.2 General Procedure for Reduction of Adducts (**3.10**) and (**3.11**) with Sodium Borohydride

N-[1-(benzotriazol-1-yl)alkyl]thioamide adduct (**3.10**) or N-[1-(benzotriazol-1-yl)alkyl]thiourea (**3.11**) (3 mmol) were taken up in 30 ml of dry tetrahydrofuran, and sodium borohydride (3 mmol) was added in one portion at room temperature. After 30 minutes of reflux, the solvent was removed (30°C/25 mmHg). The residue was treated with 30 ml of water and extracted with chloroform (3 x 30 ml). The organic layer was washed with 2N NaOH (30 ml), water (30 ml) and dried with $MgSO_4$ (10 g). Evaporation of the solvent (25°C/25 mmHg) yielded the N-alkylthioamides.

N-Methylthiobenzamide (**3.14.1**)

Prepared (98%) from (**3.10.1**), as a solid, m.p. 77-80°C {lit. m.p. 79-80°C (micro-crystals from ethanol) [76ACS(B)837]} (Found: C, 63.5; H, 6.0; N, 9.3. C_8H_9NS requires: C, 63.5; H, 6.0; N, 9.3%); ν_{max} (nujol) 3300w, 1640w cm^{-1}; δ_H ($CDCl_3$) 8.24 (1 H, broad, NH), 7.66-7.61 (2 H, m, H-2,6), 7.36-7.23 (3 H, m, H-3,4,5), 3.17 (3 H, d, J = 4 Hz, -CH_3); δ_C ($CDCl_3$) 199.4 (C=S), 141.0, 130.7, 128.1, 126.4, 33.3 (N-CH_3).

N-(2-methylpropyl)thiobenzamide (**3.14.2**)

Prepared (99%) from (**3.10.2**), as an oil, (Found: M^+, 193.0922, calculated for $C_{11}H_{15}NS$: M^+, 193.0925); ν_{max} (neat) 3240s, 1640w cm^{-1}; δ_H ($CDCl_3$) 8.22 (1 H, broad, NH), 7.64-7.58 (2 H, m, H-2,6), 7.40-7.20 (3 H, m, H-3,4,5), 3.51 (2 H, dd, J = 7 Hz,-CH_2-NH), 2.17-1.96 (1 H, m, -CH), 0.91 (6 H, d, J = 7 Hz, 2 -CH_3); δ_C ($CDCl_3$) 197.3 (C=S), 140.9, 130.4, 127.7, 126.2, 53.4 (-CH_2-NH), 26.8, 20.0, 19.9.

N-(1-Hexyl)thiobenzamide (**3.14.3**)

Prepared (92%) from (**3.10.4**), as an oil, (Found: M^+, 221.1235, calculated for $C_{13}H_{19}NS$: M^+, 221.1238); ν_{max} (neat) 3250s, 1520s cm^{-1}; δ_H ($CDCl_3$) 8.04 (1 H, broad, NH), 8.05-8.02 (2 H, m, H-2,6), 7.66-7.22 (3 H, m, H-3,4,5), 3.68 (2 H, q, J = 7 Hz, -CH_2-NH), 1.70-1.59 (2 H, m, -CH_2-), 1.38-1.27 (6 H, m, other methylene protons), 0.92-0.85 (3 H, m, -CH_3); δ_C ($CDCl_3$) 198.4 (C=S), 141.4, 130.5, 128.0, 126.4, 46.5 (-CH_2-NH), 31.1, 27.6, 26.4, 22.2, 13.7.

N-(1-Octyl)thiobenzamide (**3.14.4**)

Prepared (95%) from (**3.10.5**), as an oil, b.p. 194-198°C/2 mmHg {lit. b.p. 196-197°C/2 mmHg, [70MI1980]}; ν_{max} (neat) 3220s, 1520s cm^{-1}; δ_H ($CDCl_3$) 7.83 (1 H, broad, NH), 7.68-7.63 (2 H, m, H-2,6), 7.37-7.25 (3 H, m, H-3,4,5), 3.74-3.70 (2 H, m, -CH_2-NH), 1.69-1.68 (2 H, m, -CH_2-), 1.27 (10 H, m, other methylene protons), 0.88-0.85

(3 H, m, -C<u>H</u>$_3$); δ_C ($CDCl_3$) 198.7 (C=S), 141.7, 130.9, 128.2, 126.5, 46.7 (-C<u>H</u>$_2$-NH), 31.6, 29.1, 29.0, 27.9, 26.9, 22.4, 13.9.

N-(1-Nonyl)thiobenzamide (**3.14.5**)

Prepared (97%) from (**3.10.6**), as an oil, (Found: M^+, 263.1677, calculated for $C_{16}H_{25}NS$: M^+, 263.1707); ν_{max} (neat) 3250s, 1525s cm^{-1}; δ_H ($CDCl_3$) 8.04 (1 H, broad, N<u>H</u>), 7.62 (2 H, d, J = 8 Hz, H-2,6), 7.36-7.22 (3 H, m, H-3,4,5), 3.67 (2 H, q, J = 7 Hz, -C<u>H</u>$_2$-NH), 1.69-1.62 (2 H, m, -C<u>H</u>$_2$-), 1.27 (12 H, m, other methylene protons), 0.88-0.84 (3 H, m, -C<u>H</u>$_3$); δ_C ($CDCl_3$) 198.3 (C=S), 141.4, 130.5, 127.9, 126.4, 46.5 (-C<u>H</u>$_2$-NH), 31.5, 29.1, 28.95, 28.9, 27.6, 26.7, 22.3, 13.8.

N-(2-Methylpropyl)thiourea (**3.15.1**)

Prepared (60%) from (**3.11.1**), as a solid, m.p. 99-101°C {lit. m.p. 100-101°C (prisms from water) [53ACS(2)528]}; δ_H (Me_2SO-d_6) 7.58-6.84 (3 H, m, N<u>H</u>$_2$ and N<u>H</u>), 3.19 (2 H, m, -C<u>H</u>$_2$-NH), 1.80 (1 H, m, -C<u>H</u>-), 0.87 (6 H, d, J = 7 Hz, 2 -C<u>H</u>$_3$); δ_C (Me_2SO-d_6) 183.3 (C=S), 51.5 (-C<u>H</u>$_2$-NH), 27.7, 20.0, 19.95.

N-(1-Octyl)thiourea (**3.15.2**)

Prepared (60%) from (**3.11.2**), as a solid, m.p. 98°C {lit. m.p. 96-98°C (plates from Pet.Ether/EtOH) [61JAP13642]}; δ_H ($CDCl_3$) 6.31 (1 H, broad, N<u>H</u>), 3.43 (2 H, m, -C<u>H</u>$_2$-NH), 1.61 (2 H, t, J = 6 Hz, -C<u>H</u>$_2$-), 1.29 (12 H, m, other methylene protons and N<u>H</u>$_2$), 0.89 (3 H, m, -C<u>H</u>$_3$); δ_C ($CDCl_3$) 181.3 (C=S), 44.4 (-C<u>H</u>$_2$-NH), 31.7, 29.1, 28.95, 26.8, 22.5, 13.9.

3.4.3 General Procedure for Preparation of Secondary Thioamides by Reaction of Adducts (**3.10**) with Grignard Reagents

To the Grignard reagent prepared from magnesium turnings (10.5 mmol) and an alkyl or an aryl halide (10.5 mmol) in diethyl ether (20 ml) N-[1-(benzotriazol-1-yl)alkyl]-thioamide (5 mmol) in tetrahydrofuran (15 ml) was added dropwise. After addition was

completed the reaction mixture was refluxed for 1 h and then poured onto ice-water (20 g) and NH_4Cl (15 ml, saturated solution). The organic layer was washed with 1N NaOH (2 x 15 ml), water (2 x 20 ml) and dried with $MgSO_4$ (5 g). Evaporation of the solvent (25°C/35 mmHg) gave the crude product which was then purified.

N-Benzylthiobenzamide (**3.16.1**)

Prepared (84%) from (**3.10.1**) and benzylmagnesium chloride, as an oil, purified by column chromatography on silica gel, using chloroform; (Found: M^+, 241.0919, calculated for $C_{15}H_{15}NS$: M^+, 241.0925); ν_{max} ($CHBr_3$) 3380s, 1520s cm^{-1}; δ_H ($CDCl_3$) 7.60 (2 H, d, J = 6 Hz, H-2,6), 7.40-7.17 (9 H, m, other aromatic protons and NH), 4.10-3.99 (2 H, m, -CH_2-NH), 3.08-2.99 (2 H, m, -CH_2-); δ_C ($CDCl_3$) 199.1 (C=S), 141.7, 138.1, 130.9, 128.8, 128.7, 128.4, 126.5, 47.4 (-CH_2-NH), 33.7.

N-[(α-Benzyl)-2-methylpropyl]thiobenzamide (**3.16.2**)

Prepared (87%) from (**3.10.2**) and benzylmagnesium chloride, as an oil, purified by column chromatography on silica gel using chloroform; (Found: M^+, 283.1393, calculated for $C_{18}H_{21}NS$: M^+, 283.1394); ν_{max} (KBr) 3360w, 1508s cm^{-1}; δ_H ($CDCl_3$) 7.54-7.17 (11 H, m, all aromatic protons and NH), 5.00-4.86 (1 H, m, -CH-NH), 3.00-2.94 (2 H, m, -CH_2-Ph), 2.12-2.01 (1 H, m, -CH-), 1.02 (6 H, d, J = 7 Hz, 2 -CH_3); δ_C ($CDCl_3$) 198.8 (C=S), 142.3, 137.5, 130.5, 129.0, 128.4, 128.3, 128.1, 126.3, 61.3 (-CH-NH), 35.9, 29,9, 19.2, 18.0.

N-(4-Octyl)thiobenzamide (**3.16.3**)

Prepared (89%) from (**3.10.3**) and n-butylmagnesium bromide, as an oil, purified by column chromatography on silica gel using chloroform; (Found: M^+, 249.1546, calculated for $C_{15}H_{23}NS$: M^+, 249.1551); ν_{max} (neat) 3240s, 1520s cm^{-1}; δ_H ($CDCl_3$) 7.65 (2 H, d, J = 7 Hz, H-2,6), 7.54-7.27 (4 H, m, other aromatic protons and NH), 4.78-4.73 (1 H, m, -CH-NH), 1.70-1.27 (10 H, m, other aliphatic protons), 0.97-0.86 (6 H, m, 2 -CH_3); δ_C

($CDCl_3$) 197.8 (C=S), 141.8, 130.1, 127.7, 126.0, 55.4 (-CH-NH), 35.7, 33.3, 27.4, 22.1, 18.6, 13.5, 13.4.

N-[(α-Phenyl)-1-pentyl]thiobenzamide (**3.16.4**)

Prepared (88%) from (**3.10.4**) and phenylmagnesium bromide, as an oil, purified by column chromatography on silica gel using chloroform; (Found: M^+, 297.1537, calculated for $C_{19}H_{23}NS$: M^+, 297.1551); ν_{max} (neat) 3250m, 1520s cm^{-1}; δ_H ($CDCl_3$) 7.90 (1 H, d, J = 7 Hz, NH), 7.64 (2 H, d, J = 10 Hz, H-2,6), 7.42-7.21 (8 H, m, other aromatic protons), 5.73 (1 H, m, -CH-NH), 2.06-2.05 (2 H, m, $-CH_2-$), 1.97-1.22 (6 H, m, other aliphatic protons), 0.89-0.83 (3 H, m, $-CH_3$); δ_C ($CDCl_3$) 198.0 (C=S), 141.9, 140.4, 130.7, 128.6, 127.5, 126.9, 126.5, 59.7 (-CH-NH), 35.0, 31.3, 25.7, 22.3, 13.8.

N-[(α-Benzyl)-1-undecyl]thiobenzamide (**3.16.5**)

Prepared (81%) from (**3.10.7**) and benzylmagnesium chloride, as an oil, purified by column chromatography on silica gel using chloroform, (Found: M^+, 395.2633, calculated for $C_{26}H_{37}NS$: M^+, 395.2646); ν_{max} (neat) 3200s, 1530m cm^{-1}; δ_H ($CDCl_3$) 9.74 (1 H, d, J = 8 Hz, NH), 7.64 (2 H, d, J = 7 Hz, H-2,6), 7.27-7.26 (8 H, m, other aromatic protons), 5.00-4.90 (1 H, m, -CH-NH), 3.27-2.80 (2 H, m, $-CH_2-$), 2.76-0.87 (23 H, other aliphatic protons); δ_C ($CDCl_3$) 196.3 (C=S), 141.1, 137.3, 128.6, 128.5, 127.8, 126.8, 126.2, 125.9, 124.7, 55.9 (-CH-NH), 38.1, 31.4, 30.3, 28.0, 27.9, 27.8, 24.7, 21.1, 12.7.

2,4,5-Triphenyl-1*H*-imidazole

Prepared (45%) by refluxing benzotriazole (11.9 g, 0.1 mol), benzaldehyde (10.6 g, 0.1 mol), and thiobenzamide (13.7 g, 0.1 mol) after 10 hours, as a solid, m.p. 273-275°C (needles from ethanol) {lit. m.p. 275°C [82ZOU(18)2273]}, (Found: M^+, 296.1304, calculated for $C_{21}H_{16}N_2$: M^+, 296.1313), (Found: C, 85.0; H, 5.65; N, 9.3. $C_{21}H_{16}N_2$ requires: C, 85.1; H, 5.4; N, 9.45%); ν_{max} (nujol) 3080w, 2950s, 1605m, 1450s cm^{-1}; δ_H

(Me_2SO-d_6) 8.13 (2 H, d, J = 8 Hz), 7.58-7.28 (13 H, m), 3.25 (1 H, broad signal, NH); δ_C (Me_2SO-d_6) 145.6 (C-2 of imidazole), 130.4 (C-4, C-5 of imidazole), 128.7, 128.4, 128.2, 127.8, 127.1, 125.2.

CHAPTER IV
N-FUNCTIONALIZATION OF HETEROCYCLES *VIA* LITHIATION AND ELECTROPHILIC SUBSTITUTION

4.1 Introduction

4.1.1 General Overview on the Formation and Stability of α-Heterocarbanions

Recently, chemical transformations involving lithiation and subsequent electrophilic substitution on carbons alpha to heteroatoms have become very interesting from both mechanistic and synthetic points of view. The challenging part of such transformations is formation of the α-heterocarbanions. The most common method of generating carbanions is proton abstraction using organometallic reagents, in particular organolithiums. Such processes are called metallation, or in cases when a proton is replaced by lithium - lithiation [54OR(8)258, 79OR(26)1] (Scheme 4.1). There are several factors that must be considered in attempts to form carbanions alpha to heteroatoms.

Scheme 4.1

First of all, CH protons alpha to a heteroatom are not always very acidic. Therefore, relatively strong bases are required to abstract the protons. Many lithiating reagents have been developed over the years and these can be divided in two groups. The first group includes aryl- and alkyl-lithiums. These reagents coordinate with ethers and form oligomers of varying complexity in solution [for reviews see 62JA(84)1371, 70PAC(23)447, 73JOM(54)1, 74MI38, 84PAC(56)151]. They become more basic as the size of the aggregate decreases and usually THF is the solvent of choice for generating reactive species [64JA(86)2076, 70JA(92)4664]. The other group of lithiating reagents includes n-butyllithium complexes with amines (TMEDA) and lithium dialkylamides.

A second factor concerns stabilization and destabilization of α-heterocarbanions by adjacent groups. Formation of the negative charge is inhibited in cases where the adjacent heteroatom carries an electron pair on nitrogen or oxygen. Such atoms destabilize the carbanionic center. Attachment of the carbanion to atoms such as sulfur or phosphorus usually increases the stability of the carbanion, although the explanation is still in dispute [75JA(97)2209, 76JA(98)5435, 76JA(98)7498, 78JA(100)1604, 83TL3789, 83TL4071].

4.1.2 Activation of α-Methylene Protons by a Heterocyclic Moiety

Metallation of N-alkylheterocycles followed by reaction with electrophiles has attracted much attention recently [79OR(26)1]. Examples include pyridone [80JCS(P1)2851] and quinazoline derivatives [82JCR(S)26] as well as 1-methylimidazole [83JCR(S)196] and 1,2-dimethylimidazole [83JCS(P1)271]. A considerable amount of work has also been done in our laboratory concerning activation of the methylene protons alpha to a nitrogen incorporated in a five-membered heterocyclic ring such as N-alkyl-pyrazoles [83T(39)2023, 83T(39)4133] (Figure 4.1). Metallation of N-alkyl-

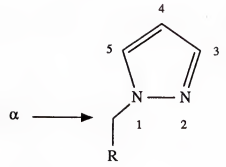


Figure 4.1

heterocycles usually results in the replacement of a single ring proton although in some cases mixtures of products are obtained [53JA(75)375, 71CJC(49)2139, 72JOC(37)215,

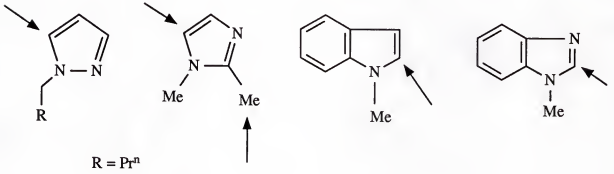


Figure 4.2

73CB(106)2815, 76JOC(41)163, 83T(39)2023, 87JCS(P1)775] (Figure 4.2). Therefore, in order to provide better regioselectivity at C-α, other carbanion stabilizing substituents must be introduced. An aryl substituent has been used successfully to facilitate lithiation

in N-benzylimidazole [74JOC(39)1374, 84JCS(P1)481], and N-arylmethyl-imidazoles and -triazoles [85S302]. Other activating groups include a second nitrogen linked heterocyclic ring as in methylenebispyrazoles [83T4133]; phenylthio groups as in 1-(phenylthio-methyl)benzimidazole [87JCS(P1)775], 9-(phenylthiomethyl)carbazole [85JOC(50)1351],

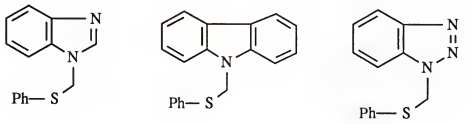


Figure 4.3

and 1-(phenylthiomethyl)benzotriazole [87JCS(P1)781] (Figure 4.3). More recently, a trimethylsilyl group has also been used as an activating substituent in 1-(trimethyl-silylmethyl)benzotriazole [88UP2] (Figure 4.4).

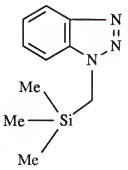


Figure 4.4

4.1.3 Acidity Measurements for Protons in Heterocyclic Rings

Since metallation of organic compounds has become a useful synthetic tool, it is important to determine which metallation reagent to use for best selectivity of the reaction. A knowledge of the acidity of the proton to be removed is thus useful in the selection of this base.

Development of an acidity scale for weak carbon acids has been an area of interest for many years. The fundamental research of Cram [65MI19] and Streitwieser [80MI19, 81JA(103)6443] developed acidity measurements in a variety of solvents. A new scale was established by Bordwell in pure DMSO as a solvent [81JOC(46)632]. The pK_a values of hydrogens attached to carbon atoms that are part of a heterocyclic ring have been

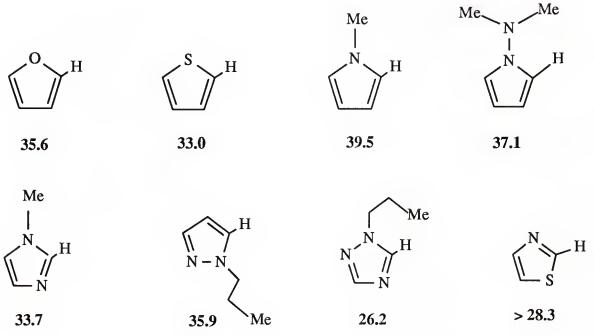
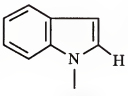
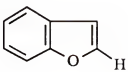


Figure 4.5

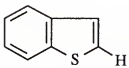
studied recently. Heterocyclic rings such as those of benzothiazole, N-alkyl-imidazoles, -1,2,4-triazoles, or -pyrroles [see parts (1-5): 82TL4195, 83CJC(61)2729, 83CC620, 84JOC(49)3442, 85CJC(63)3505] were deprotonated between -60°C and 25°C by lithium amides in THF. Measurement of the change in carbon chemical shifts of the resultant lithium salts yielded pK_a values. The pK_a data for monocyclic five-membered rings are given in Figure 4.5 [85CJC(63)3505]. There is a significant strengthening effect by the heteroatom on the adjacent C-H bond. The magnitude of this effect is in the order S > O > N. The effect of a second nitrogen is appreciable (N-methylimidazole *versus* N-methylpyrrole). An attached benzene ring has a small effect and tends to damp the effect of the heteroatom (Figures 4.5 *versus* 4.6). From the data presented in Figures 4.5



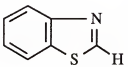
38.1



33.2



33.5



< 28.9

Figure 4.6

and 4.6 it can be concluded, that in the examples studied, the preferred lithiation site has been at the carbon adjacent to the heteroatom or in between two heteroatoms, whenever such a position was present. There were several examples in which more than one site was attacked by the lithiating reagent.

Recent work of Katritzky *et al.* showed that lithiation of N-protected heterocycles (aminals) of imidazole, benzimidazole, and pyrazole occurred at the 2-position (Figure 4.7) [88JOCIP1]. Carbazole and benzocarbazole aminals underwent metallation at the aromatic CH nearest to the aromatic nitrogen [88JOC(53)794] (Figure 4.8).

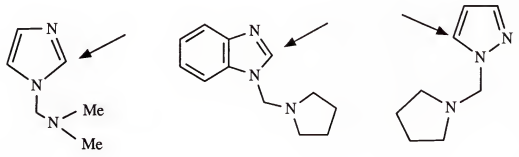


Figure 4.7

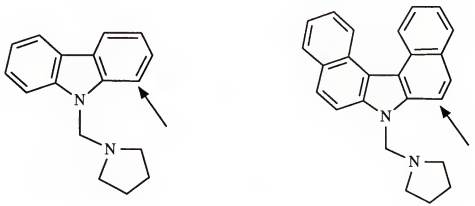


Figure 4.8

4.1.4 Aim of the Work

The goal of this work was to investigate the ability of benzotriazole to activate the alpha protons in unsymmetrical biheterocyclic systems connected *via* a methylene bridge (Figure 4.9).

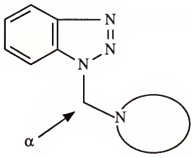
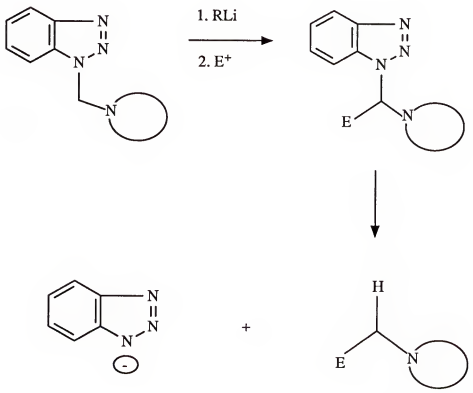


Figure 4.9

This type of heterocyclic aminal, in which a methylene group links two pyrrole-like heterocyclic nitrogen atoms, is not easily accessible by classical synthetic methods. In 1982, Elguero and coworkers [82JHC(19)1141] reported the synthesis and an NMR study of several aminals in which the two heterocyclic rings were identical. These compounds were prepared by reactions of azoles with methylene chloride under phase transfer catalysis conditions in yields of 22 to 88%. Further transformations of such products were not reported at that time. Examples of a different type of heterocyclic aminal, N,N-dialkylaminomethyl heterocycles, were used in our laboratory for reactions in which the dialkylaminomethyl function served as a protecting substituent for the heterocyclic nitrogen atoms of carbazole, benzocarbazoles [88JOC(53)794], and for other

systems [88JOCIP1]. In each case, the dialkylamino group simultaneously activated a ring CH to lithiation.

We believed that N-(benzotriazol-1-ylmethyl) heterocycles could open new routes for synthetic transformations. In particular, the benzotriazole moiety, because of its electron-withdrawing character, should increase the acidity of the α-CH_2 protons and thus facilitate metallation at the α-carbon. Consequent removal of the protecting benzotriazole should also be possible since benzotriazole has been shown to be a good leaving group [87JCS(P1)805, 819] (Scheme 4.2).

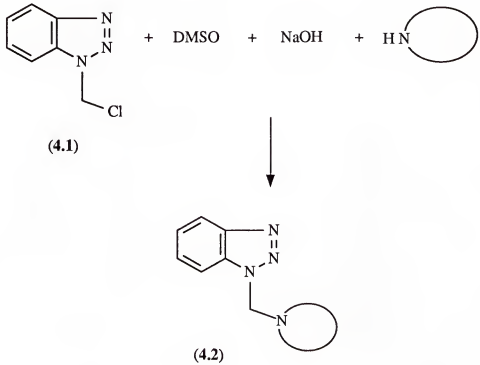


Scheme 4.2

4.2 Results and Discussion

4.2.1 Preparation of N-(Benzotriazol-1-ylmethyl) Heterocycles (**4.2**)

Two alternative sets of conditions were used for the preparation of N-(benzotriazol-1-ylmethyl) heterocycles. Both procedures utilized 1-chloromethylbenzotriazole (**4.1**) and the sodium salt of the corresponding nitrogen heterocycle. 1-Chloromethylbenzotriazole was easily prepared by heating a solution of 1-hydroxymethylbenzotriazole and thionyl chloride in benzene under reflux {modified version of a literature procedure [52JA(74)3868]}. The NH-heterocycles were heated in DMSO with powdered sodium hydroxide and 1-chloromethylbenzotriazole. Cooling and treatment with ice-water gave the adducts (**4.2**) (Scheme 4.3) (Table 4.1).



(**4.1**)

(**4.2**)

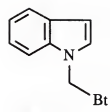
Scheme 4.3

Alternatively, the sodium salt of the NH-heterocycle was formed with sodium ethanolate, these yields being slightly lower in most of the cases. The 2-thiobenzothiazole gave the corresponding S-adduct (**4.2.8**). All crude products were purified by recrystallization from the appropriate solvent (Table 4.1).

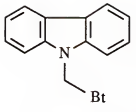
Table 4.1 Preparation of N-(Benzotriazol-1-ylmethyl) Heterocycles (**4.2**)

Product	Heterocycle	Yield (%)	M.p. (°C)	Recryst. solvent	Crystal form
(**4.2.1**)	Indole	84	176-178	EtOH	Needles
(**4.2.2**)	Carbazole	87	195-197	Benzene	Prisms
(**4.2.3**)	Benzimidazole	80	198-199	EtOH	Needles
(**4.2.4**)	2-Methylbenzimidazole	78	182-184	MeOH	Prisms
(**4.2.5**)	2-Phenylbenzimidazole	89	191-192	MeOH/Me_2CO	Prisms
(**4.2.6**)	Imidazole	62	108-112	EtOAc	Prisms
(**4.2.7**)	1,2,4-Triazole	82	137-138	EtOH	Prisms
(**4.2.8**)	2-Thiobenzothiazole	93	116-118	Benzene	Plates

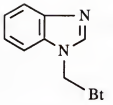
The structures of all adducts (**4.2**) (Figure 4.10) were confirmed by their spectral and analytical properties (see Experimental for details). The ^{13}C NMR spectra showed the characteristic pattern for a 1-substituted benzotriazole as well as for an N-substituted heterocycle. Thus the quaternary carbons C-3a and C-7a of the benzotriazole moiety appeared at δ 145.8-143.9 ppm and δ 132.4-131.8 ppm respectively. The most indicative chemical shift was the one corresponding to the methylene carbon between two hetero-



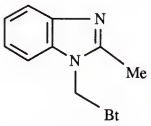
(4.2.1)



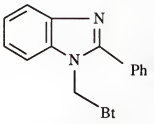
(4.2.2)



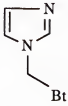
(4.2.3)



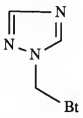
(4.2.4)



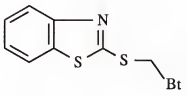
(4.2.5)



(4.2.6)



(4.2.7)



(4.2.8)

Bt = 1-Benzotriazolyl

Figure 4.10

cycles. This peak appeared in the region δ 58.0-48.7 ppm (Table 4.2). The proton spectra of the N-(benzotriazol-1-ylmethyl) heterocycles were not very informative because the methylene protons were deshielded into the aromatic region and appeared together with other aromatic protons.

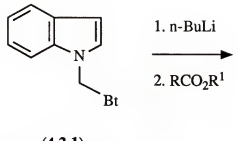
Table 4.2 ^{13}C NMR Chemical Shifts for the Benzotriazole Ring Carbons and Methylene Groups in Adducts (**4.2**)

Prod	C-3a	C-4	C-5	C-6	C-7	C-7a	CH_2
(**4.2.1**)	145.3	119.3	124.4	128.9	110.6	132.1	56.8
(**4.2.2**)	145.6	119.9	124.1	127.8	109.5	132.1	55.3
(**4.2.3**)	145.3	119.6	124.3	128.0	110.2	132.0	54.7
(**4.2.4**)	145.1	118.4	124.0	127.8	109.5	131.9	53.9
(**4.2.5**)	145.7	120.0	124.3	128.1	111.0	131.8	55.3
(**4.2.6**)	145.8	119.5	124.7	128.4	110.6	132.4	56.5
(**4.2.7**)	145.1	119.3	124.4	128.0	110.6	132.3	58.0
(**4.2.8**)	145.2	119.1	124.0	127.3	111.0	132.2	48.7

4.2.2 Reactions of Lithiated Indole and Carbazole Adducts (**4.2.1**) and (**4.2.2**) with Electrophiles

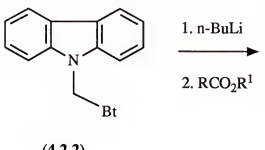
4.2.2.1 Esters as Electrophiles

The indole (**4.2.1**) and carbazole adducts (**4.2.2**) underwent smooth lithiation with n-butyllithium or LDA in THF at -78°C to form deeply colored carbanions. Electrophiles were added at -78°C and the mixtures allowed to warm up overnight. Esters of carboxylic acids (aliphatic and aromatic) reacted rapidly with the lithium salts of both indole and carbazole adducts (**4.2.1**) and (**4.2.2**) forming products (**4.2.1.1**)-(**4.2.1.3**), (**4.2.2.1**), (**4.2.2.3**), and (**4.2.2.4**) with acyl or aroyl groups on the methylene bridge carbon in good yields (Scheme 4.4).



(**4.2.1**)

(**4.2.1.1**) R = Ph
(**4.2.1.2**) R = Pr^i
(**4.2.1.3**) R = Pr^n



(**4.2.2**)

(**4.2.2.1**) R = Ph
(**4.2.2.2**) R = Pr^n
(**4.2.2.3**) R = Et

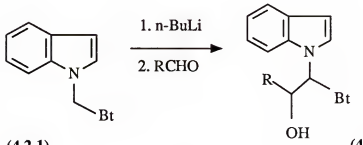
Bt = 1-Benzotriazolyl

Scheme 4.4

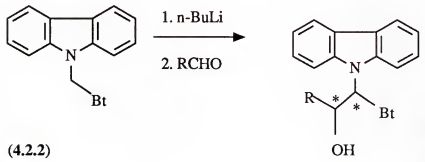
Structures of all new compounds were characterized by their spectral properties and supported by analytical data. The ^{13}C NMR spectra revealed new features that allowed structure assignment. The acyl and aroyl adducts had chemical shifts for the carbonyl carbon in the region of δ 202.9 - 187.5 ppm. The methine carbon alpha to both heterocyclic nitrogens was observed downfield at δ 71.3 - 69.4 ppm. The chemical shifts of the carbons in the heterocyclic rings resembled the typical pattern for the N-substituted benzotriazole, indole, and carbazole.

4.2.2.2 Aliphatic and Aromatic Aldehydes as Electrophiles

Similarly, addition of aliphatic or aromatic aldehydes resulted in formation of the hydroxy compounds (**4.2.1.4**) and (**4.2.2.4**) (Scheme 4.5) (Table 4.3). Lithiation of N-(1-benzotriazol-1-ylmethyl)carbazole (**4.2.2**) followed by addition of butyraldehyde led to a mixture of two diastereoisomeric alcohols. These compounds were partially separated by column chromatography and their structures assigned on the basis of spectral and analytical data. An approximate ratio of the two isomers was obtained from analysis of the ^{1}H NMR spectra of the mixture.



(**4.2.1**) (**4.2.1.4**) R = p-Me-Ph



(**4.2.2**) (**4.2.2.4a**) R = Pr^n

(**4.2.2.4b**) R = Pr^n

Scheme 4.5

Both alcohols (**4.2.2.4a**) and (**4.2.2.4b**) showed two characteristic peaks in the ^{13}C NMR spectra that corresponded to the two methine carbons of the two diastereoisomers respectively. The signal for the carbon carrying the hydroxy group appeared about one ppm downfield from the signal for the carbon alpha to both heterocycles. The patterns for the carbons of benzotriazole and carbazole were not affected significantly (see Experimental for details). The ^1H NMR spectra of the alcohols were used to determine the ratio of two isomers in the mixture. The signal corresponding to the protons bonded to the carbon bearing the hydroxy group appeared downfield as a complex multiplet. The protons alpha to the heterocyclic rings were not deshielded as much and was observed at δ 4.41 ppm and δ 3.31 ppm as well resolved doublets with coupling constants 5 and 4 Hz respectively (Figure 4.10).

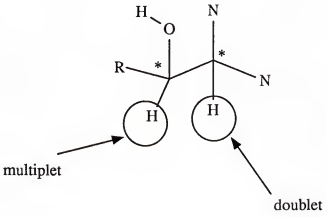


Figure 4.10

Stereochemical assignments for alcohols, based on this example would be tenuous. More examples would be needed in order to determine the stereoselectivity of this reaction. As will be shown in Section 4.2.5 of this Chapter, mixtures of diastereoisomeric alcohols were also obtained as a result of sodium borohydride reduction of the acyl derivatives of the indole and carbazole (**4.2.1**) and (**4.2.2**).

4.2.2.3 Benzyl Bromide as an Electrophile

Reaction of (**4.2.1**) with LDA followed by treatment with benzyl bromide led to the corresponding α-benzylated product (**4.2.1.5**) in yield of 86% (Scheme 4.6).

(**4.2.1**) (**4.2.1.5**)

Scheme 4.6

The use of n-BuLi as a proton abstracting reagent, followed by addition of benzyl bromide gave a lower yield and much less pure product. In the ^{13}C NMR spectrum of (**4.2.1.5**) the methylene carbon appeared at δ 39.1 ppm and the chemical shift of the methine carbon was δ 70.1 ppm. This result was confirmed by an APT experiment. In the ^{1}H NMR the H-3 of the indole ring appeared as a well resolved doublet with a coupling constant of 3 Hz, while the methine proton was indistinguishable from other aromatic protons that were

seen as a complicated multiplet. The diastereotopic methylene protons split each other into doublets that were additionally split by the methine proton and resulted in an eight-line signal at δ 4.14 ppm.

Table 4.3 Reaction of (**4.2.1**) and (**4.2.2**) with n-BuLi and Electrophiles

Product	Electrophile	Yield (%)	M.p. (°C)	Recr.[a] solv.	Elemental analysis C Found/Calculated	H	N
(4.2.1.1)	$PhCO_2Et$	81	191-193	A	74.6	4.6	15.9
					75.0	4.6	15.9
(4.2.1.2)	Me_2CHCO_2Et	95	138-140	A	71.3	5.7	17.4
					71.7	5.7	17.6
(4.2.1.3)	Pr^nCO_2Et	75	144-146	B	71.9	5.7	18.0
					71.7	5.7	17.6
(4.2.1.4)	p-Me-PhCHO	68	224-226	A	74.6	5.5	15.5
					75.0	5.5	15.2
(4.2.1.5)[b]	$PhCH_2Br$	86	107-109	A	78.3	5.4	16.2
					78.1	5.4	16.6
(4.2.2.1)	$PhCO_2Et$	88	89-91	A	77.2	4.6	13.6
					77.6	4.5	13.9
(4.2.2.2)	Pr^nCO_2Et	84	189-192	C	75.0	5.6	15.2
					75.0	5.5	15.2
(4.2.2.3)	$EtCO_2Me$	68	176-178	B	74.7	5.2	15.7
					74.6	5.1	15.8
(4.2.2.4a)	Pr^nCHO	67	177-179	B	74.7	6.0	15.2
					74.6	6.0	15.2
(4.2.2.4b)	Pr^nCHO	8	189-194	B	74.4	6.0	15.1
					74.6	6.0	15.2

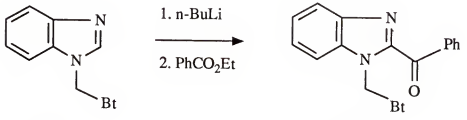
[a]Recrystallizing solvent systems: A: Et_2O-Pet.Ether; B: Ethanol; C: Ethanol-Acetone

[b]LDA was used as a base.

4.2.3 Lithiation of Benzimidazole and Imidazole Derivatives and Consequent Reaction with Electrophiles

Lithiation of 1-substituted imidazoles or benzimidazoles occurs at the 2-position if it is free [58JOC(23)1791, 70OR(26)1, 84TL1957]. If the 2-position is substituted, the preferred site of lithiation depends upon the nature of the 2-substituent [73JOC(38)4379, 78CI(L)582].

With n-BuLi (THF, -78°C), the benzimidazole adduct (**4.2.3**) underwent lithiation and subsequent reaction with ethyl benzoate at the 2-position of the heterocyclic ring to give product (**4.2.3.1**) (Scheme 4.7).

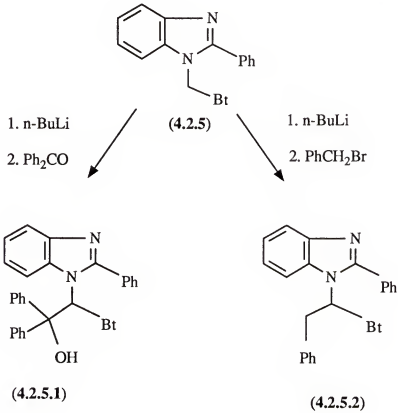


(**4.2.3**) (**4.2.3.1**)

Scheme 4.7

The reaction of 2-methylbenzimidazole (**4.2.4**) and ethyl benzoate gave starting material or complicated mixtures under various conditions. However, the 2-phenyl-benzimidazole adduct (**4.2.5**), on lithiation with n-BuLi and subsequent reaction with benzophenone or benzyl bromide gave the expected products (**4.2.5.1**) and (**4.2.5.2**), respectively (Scheme 4.8). In the ^{13}C NMR spectra of both compounds (**4.2.5.1**) and (**4.2.5.2**), the C-2 of the substituted benzimidazole was the most deshielded carbon and appeared at δ 153.4 ppm. Additionally, a typical pattern for 1-substituted benzotriazoles and 1,2-substituted benzimidazoles was observed. The product (**4.2.5.1**) displayed two

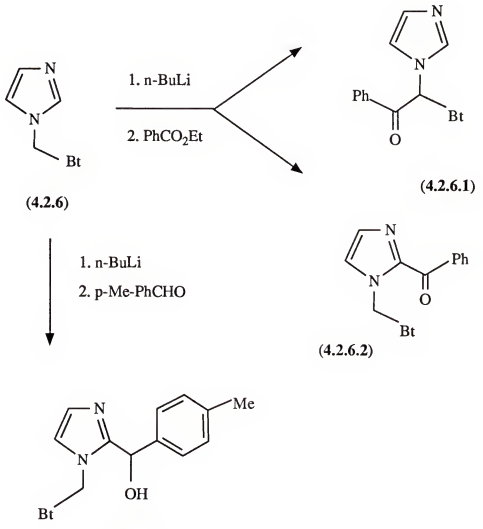
chemical shifts in the aliphatic region at δ 83.4 ppm and δ 73.0 ppm. They were assigned to the quaternary carbon bearing the hydroxy group and to the methine carbon bonded to the heterocyclic rings respectively. In the ^{13}C NMR spectrum of **(4.2.5.2)**, the chemical shifts of the two aliphatic carbons were observed at δ 69.8 ppm (CH) and δ 38.1 ppm (CH_2) respectively.



Scheme 4.8

N-(Benzotriazol-1-ylmethyl)imidazole **(4.2.6)**, when lithiated with n-BuLi and treated with ethyl benzoate at -78°C, gave a mixture of alpha- and 2-substituted products **(4.2.6.1)** and **(4.2.6.2)**. These two isomeric compounds were separated by column chromatography. The 2-substituted product **(4.2.6.2)** was less polar and could be

distinguished from the alpha substituted isomer on the basis of its ^{13}C NMR spectrum. The chemical shift of the methylene carbon in (**4.2.6.2**) appeared at 56.9 ppm while the methine carbon in (**4.2.6.1**) was at 69.6 ppm. There was a significant difference in the melting points between the two products (Table 4.4). Treatment of (**4.2.6**) with n-BuLi followed by p-methylbenzaldehyde yielded only the 2-substituted product (Scheme 4.9).



(**4.2.6**)

(**4.2.6.1**)

(**4.2.6.2**)

(**4.2.6.3**)

Scheme 4.9

The alcohol (**4.2.6.3**) showed the characteristic ^{13}C NMR resonances corresponding to the aliphatic carbons. Thus, the unsubstituted methylene carbon appeared at δ 56.3 ppm, whereas the methine carbon, bearing the hydroxy group was observed at δ 68.7 ppm. The assignment of the peaks was confirmed by an APT experiment.

Table 4.4 Preparation of the Derivatives of Benzimidazole and Imidazole

Product	Electrophile	Yield (%)	M.p. (°C)	Elemental analysis Found / Calculated C	H	N
(**4.2.3.1**)	$PhCO_2Et$	78	137-139	71.2 71.4	4.3 4.3	19.8 19.8
(**4.2.5.1**)	Ph_2CO	79	159-162	78.1 78.1	4.9 5.0	13.9 13.8
(**4.2.5.2**)	$PhCH_2Br$	83	176-178	78.1 78.1	5.1 5.1	16.7 16.9
(**4.2.6.1**)	$PhCO_2Et$	53	58-62	67.0 67.3	4.4 4.3	23.0 23.1
(**4.2.6.2**)	$PhCO_2Et$	30	113-114	67.7 67.3	4.3 4.3	23.4 23.1
(**4.2.6.3**)	p-Me-PhCHO	74	89-91	67.4 67.7	5.3 5.4	22.0 21.9

Very complex mixtures were obtained from N-(benzotriazol-1-ylmethyl)-1,2,4-triazole (**4.2.7**) and 2-(benzotriazol-1-ylmethyl)thiobenzothiazole (**4.2.8**) after attempted lithiation and reaction with electrophiles. Several factors could contribute to the outcome of this reactions. In the triazole adduct (**4.2.7**) there are at least two other possible sites of lithiation and that might be a reason for obtaining mixtures. In the adduct (**4.2.8**) methylene bridge connects two heteroatoms: sulfur and nitrogen. Alkyllithiums are

known to cleave carbon-heteroatom bonds to produce a new carbanion and the ease of such reaction depends on the stability of the expelled carbanion [80T(36)2531]. Nucleophilic substitution on the S-ethyl-2-thiobenzothiazole leading to the corresponding 2-lithio-derivative has been observed in various conditions [85TH119]. Similar behavior could be a possible explanation for such course of the reaction.

4.2.4 Attempted Removal of Benzotriazole

The removal of the benzotriazole moiety from compounds of the type shown below (Figure 4.11) has been achieved previously by the reaction with powdered zinc in acetic acid [88UP3].

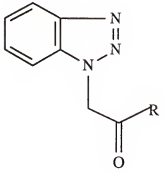
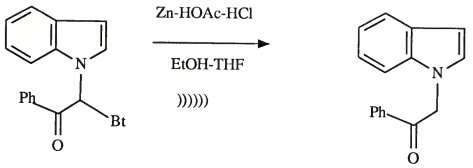


Figure 4.11

In the case of acyl and aroyl derivatives of indole and carbazole, removal of the benzotriazole protecting moiety was much more complicated. In fact, under reductive conditions (Zn/HOAc) benzotriazole was removed (43%) from (**4.2.1.1**) using an ultrasonic bath [ ))))))] and a catalytic amount of hydrochloric acid (Scheme 4.10).

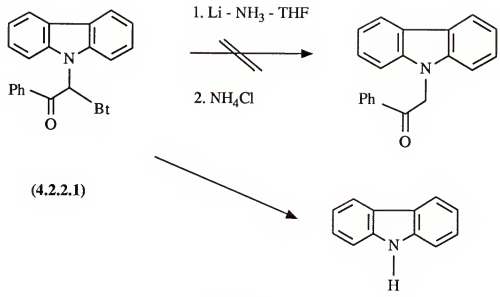


(**4.2.1.1**) (**4.3**)

Scheme 4.10

The structure of product (**4.3**) was determined from spectral and analytical data (see Experimental). Attempts to duplicate this reaction for other acyl and aroyl derivatives of indole and the carbazole series failed. There was no change (TLC) over an extended period of time, increased amount of zinc, or by addition of any acids.

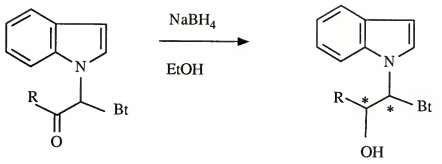
There have been many literature methods reported for the removal of functional groups alpha to the carbonyl without reduction to the alcohol [82JOC(47)2536, 83TL3477, 86JOC(51)1135]. These methods have been devoted to dehalogenation of α-haloketones [79S59, 81TL1431, 84CL2069, 85CJC(63)1263]. Attempts to apply some of these methods to our particular system failed. For example, the well known dissolving metal (Li/NH_3) reduction, when applied to carbazole derivative (**4.2.2.1**) led to carbazole as the sole isolated product (Scheme 4.11). Milder reaction conditions, like NaI/TMS-Cl [80JOC(45)3531] or NaI/H_2SO_4 [80TL3195] as applied before to remove halogen, failed and gave only unreacted starting material.



Scheme 4.11

4.2.5 Reduction of Acyl and Aroyl Derivatives of Indole and Carbazole with Sodium Borohydride

Reductive displacement of benzotriazole from other adducts (for example those from amines [87JCS(P1)805, 88JCS(P1)IP1], amides [see Chapter II], and thioamides [see Chapter III]) with sodium borohydride has been a clean, fast, and high yield reaction. We attempted to use $NaBH_4$ to the acyl and benzoyl derivatives of indole and carbazole. However, sodium borohydride could also attack the carbonyl group and give the corresponding alcohol. This reduction produced very interesting results. Treatment of the compounds derived from indole (**4.2.1.1**)-(**4.2.1.3**) with sodium borohydride in ethanol-THF mixture afforded a mixture of two products (Scheme 4.12). The reduction products were identified as alcohols that still contained the benzotriazole moiety. The reduction proceeded without any side products. Therefore, qualitative estimation of the ratio of two



R = Ph (**4.2.1.1**)
R = Pr^i (**4.2.1.2**)
R = Pr^n (**4.2.1.3**)

R = Ph (**4.2.1.6**)
R = Pr^i (**4.2.1.7**)
R = Pr^n (**4.2.1.8**)

Scheme 4.12

diastereomeric species was possible based on the ^1H NMR spectra of the crude reaction mixtures. For the mixture of alcohols (**4.2.1.6**), the ratio determined from the integration area of the two methine protons was approximately 9 to 4. This mixture was analyzed and characterized without further separation. The crude mixture of products (**4.2.1.7a**) and (**4.2.1.7b**), after preliminary examination by ^1H NMR spectroscopy (ratio 7 : 4), was then separated on the basis of differing solubility in diethyl ether. The ^1H and ^{13}C NMR data indicated that they were indeed the corresponding diastereoisomeric alcohols. There was also a significant difference in their melting points (Table 4.5). Two characteristic features were observed in their proton spectra. The signals corresponding to the CH bearing the hydroxy group appeared as complex multiplets at about 4.88 ppm for one of the isomers and at 5.33 ppm for the other. The CH bonded to the two heterocyclic rings

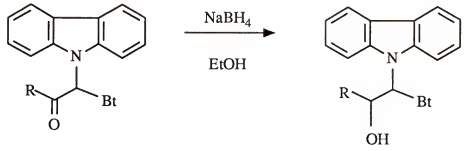
appeared at different chemical shifts for the two isomers as a doublet with a coupling constant of 6 Hz. The reduction of (**4.2.1.3**) yielded a mixture of two compounds in the ratio 7 to 6 as calculated from the initial examination of ^{1}H NMR spectra. These two compounds were separated using column chromatography. Spectral and analytical data strongly suggested that they were the two isomers (**4.2.1.8a**) and (**4.2.1.8b**). The two lower melting alcohols (**4.2.1.7a**) and (**4.2.1.8a**) were very hygroscopic.

Table 4.5 Preparation of the Diastereoisomeric Alcohols (**4.2.1.6**)-(**4.2.1.8**) and (**4.2.2.4**)

Product	Yield (%)	M.p. (°C)	Elemental analysis Found (Calculated)		
			C	H	N
(4.2.1.6)	95[a]	200-222	74.6(74.6)	5.1(5.1)	15.9(15.8)
(4.2.1.7a)	56	83-85		b	
(4.2.1.7b)	31	201-203	70.8(71.2)	6.3(6.3)	17.3(17.5)
(4.2.1.8a)	45	79-80		c	
(4.2.1.8b)	37	156-158	71.2(71.2)	6.3(6.3)	17.5(17.5)
(4.2.2.4)	99[a]	176-178	74.4(74.6)	6.0(6.0)	15.3(15.2)

[a]Yield of the mixture of isomers (otherwise the yields are given for the individual isomers) [b]Found: M^+, 320.1641, calculated for $C_{19}H_{20}N_4O$: 320.1637 [c]Found: M^+, 320.1659, calculated for $C_{19}H_{20}N_4O$: 320.1637.

The carbazole derivative (**4.2.2.2**) under these conditions yielded predominantly (9 : 1 ratio) one product (**4.2.2.4**) (Scheme 4.13). This compound was identical (melting point, TLC, spectral data) with the predominant isomer obtained earlier from the lithiation of (**4.2.2**) and reaction with butyraldehyde (see Section 4.2.2). The stereochemical assignments for all these compound might be possible with more examples and by application of Cram's rules for the sodium borohydride reduction.



R = Pr^n (**4.2.2.2**) R = Pr^n (**4.2.2.4**)

Scheme 4.13

4.3 Conclusions

All the traditional methods for removal of benzotriazole failed. Thus the development of new routes is necessary. There are several possibilities for this. Reductive methods applied to acyl and benzoyl derivatives of indole and carbazole could proceed without reduction of the carbonyl group and give the desired product directly. Another method would involve carbonyl reduction followed by a reoxidation step.

On the other hand, nucleophilic displacement at the carbon alpha to the carbonyl could be carried under basic conditions, by the classical S_N2 mechanism, where a small positive charge is developed in the transition state, however, the methine carbon is sterically hindered and thus this path is disfavored. The reaction under acidic conditions (facilitated by Lewis acid coordination with a benzotriazole nitrogen) in an S_N1 type of mechanism. This path also is disfavored because the carbonyl inhibits positive charge development. Therefore, if this analysis is correct, the most promising approach seems to be a two step sequence involving reoxidation of the carbonyl group.

4.4 Experimental

Apparatus used in this Chapter are identical to those described in Chapter III with the addition that ^{13}C NMR spectra were run, where specified, on a Varian XL300 (75 MHz) spectrometer.

Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl prior to use. Diisopropylamine was refluxed over CaH_2, distilled and stored over 4 Å molecular sieves. All moisture sensitive reactions were carried out in oven-dried (100°C overnight) apparatus under a slight positive pressure of dry argon. All transferring operations were done *via* syringes. 1-Chloromethylbenzotriazole (**4.1**) was prepared according to the modified literature procedure, m.p. 136-138°C (lit. m.p. 136-138°C [52JA(74)3868])

4.4.1 General Procedure for Preparation of N-(Benzotriazol-1-ylmethyl) Heterocycles (**4.2**)

Method A

The heterocycle (40 mmol) was dissolved in 20 ml of dimethyl sulfoxide and powdered sodium hydroxide (3.2 g, 80 mmol) was added. The suspension was heated to

60°C and then N-chloromethylbenzotriazole (6.7 g, 40 mmoles) was added in one portion. After an additional 1 hour of heating at this temperature, the mixture was cooled and poured onto 100 g of ice with rapid stirring. The solid formed was removed by filtration, washed thoroughly with cold water (3 x 100 ml) and dried. The crude product was then recrystallized from the appropriate solvent.

Method B

Sodium metal (0.92 g, 40 mmol) was dissolved in absolute ethanol (250 ml). After the exothermic reaction was completed, the corresponding heterocycle (40 mmol) was added. Then N-chloromethylbenzotriazole was added to the solution in one portion. Refluxing the solution for 30 minutes yielded a precipitate (NaCl). The solvent was removed (35°C/25 mmHg), the residue was treated with water (100 ml), and extracted with diethyl ether (3 x 100 ml). The organic layer was dried with $MgSO_4$ (20 g) and the solvent removed under vacuum (20°C/25 mmHg) yielding the crude product, which was recrystallized from the appropriate solvent.

N-(Benzotriazol-1-ylmethyl)indole (**4.2.1**)

Prepared (84%) (method A), as a solid, m.p. 176-178°C (needles from ethanol) (Found: C, 72.2; H, 4.7; N, 22.6. $C_{15}H_{12}N_4$ requires: C, 72.6; H, 4.9; N, 22.6%); δ_H (200 MHz) (Me_2SO-d_6) 8.15-8.11 (1 H, m, H-4), 8.08-8.05 (1 H, m, H-7), 7.88-7.52 (4 H, m), 7.35 (2 H, m), 7.29-7.25 (2 H, m), 7.08 (1 H, m), 6.55 (1 H, m, H-3 of indole); δ_C (50 MHz) (Me_2SO-d_6) 145.3, 135.4, 132.1, 128.95, 128.9, 128.6, 127.9, 124.4, 122.0, 120.7, 120.6, 119.3, 110.6, 110.4, 102.9, 56.8 (-$\underline{C}H_2$-).

N-(Benzotriazol-1-ylmethyl)carbazole (**4.2.2**)

Prepared (87%) (method A), as a solid, m.p. 195-197°C (prisms from benzene) (Found: C, 76.6; H, 4.7; N, 18.8. $C_{19}H_{14}N_4$ requires: C, 76.5; H, 4.7; N, 18.8%); δ_H (200 MHz) (Me_2SO-d_6) 8.05-7.91 (5 H, m), 7.72-7.68 (1 H, m), 7.52-7.20 (8 H, m); δ_C (50

MHz) ($CDCl_3$) 145.6, 139.6, 132.1, 127.8, 126.4, 124.1, 121.9, 120.6, 120.5, 119.9, 109.5, 109.0 55.3 (-$\underline{C}H_2$-).

N-(Benzotriazol-1-ylmethyl)benzimidazole (**4.2.3**)

Prepared (80%) (method B), as a solid, m.p. 198-199°C (needles from ethanol) (Found: C, 67.4; H, 4.4; N, 28.5. $C_{14}H_{11}N_5$ requires: C, 67.5; H, 4.5; N, 28.1%); δ_H (60 MHz) (Me_2SO-d_6) 8.98 (1 H, s, H-2' of benzimidazole), 8.40-7.30 (10 H, other aromatic protons and -$\underline{C}H_2$-); δ_C (75 MHz) (Me_2SO-d_6) 145.3, 143.9, 143.4, 132.7, 132.0, 128.0, 124.3, 123.1, 122.3, 119.6, 118.3, 110.7, 110.2, 54.7 (-$\underline{C}H_2$-).

N-(Benzotriazol-1-ylmethyl)-2-methylbenzimidazole (**4.2.4**)

Prepared (78%) (method A), as a solid, m.p. 182-184°C (prisms from methanol) (Found: C, 68.0; H, 4.9; N, 26.9. $C_{15}H_{13}N_5$ requires: C, 68.4; H, 5.0; N, 26.6%); δ_H (200 MHz) (Me_2SO-d_6) 7.99 (1 H, d, J = 7 Hz, H-4 of benzotriazole), 7.88-7.75 (2 H, m), 7.59-7.40 (2 H, m), 7.37-7.08 (5 H, m), 2.84 (3 H, s, -$\underline{C}H_3$); δ_C (50 MHz) (Me_2SO-d_6) 151.5 (C-2' of benzimidazole), 145.1, 141.9, 134.2, 131.9, 127.8, 124.0, 122.2, 122.1, 119.3, 118.4, 109.5, 109.4, 53.9 (-$\underline{C}H_2$-), 13.8 (-$\underline{C}H_3$).

N-(Benzotriazol-1-ylmethyl)-2-phenylbenzimidazole (**4.2.5**)

Prepared (89%) (method B), as a solid, m.p. 191-192°C (prisms from methanol/ acetone 1:1) (Found: C, 74.1; H, 4.7; N, 21.9. $C_{20}H_{15}N_5$ requires: C, 73.8; H, 4.7; N, 21.5%); δ_H (200 MHz) ($CDCl_3$) 7.96-7.91 (2 H, m), 7.82-7.53 (6 H, m), 7.38-7.15 (4 H, m), 6.97 (2 H, s, -$\underline{C}H_2$-), 6.56-6.57 (1 H, m); δ_C (50 MHz) ($CDCl_3$) 153.1 (C-2' of benzimidazole), 145.7, 142.8, 134.4, 131.8, 130.6, 129.8, 129.2, 128.6, 128.1, 124.3, 123.9, 123.5, 120.0, 119.95, 111.0, 108.6, 55.3 (-$\underline{C}H_2$-).

N-(Benzotriazol-1-ylmethyl)imidazole (**4.2.6**)

Prepared (62%) (method A), as a solid, m.p. 108-112°C (prisms from ethyl acetate) (Found: C, 60.2; H, 4.3; N, 35.2. $C_{10}H_9N_5$ requires: C, 60.3; H, 4.5; N, 35.2%); δ_H (200

MHz) (Me_2SO-d_6) 8.19-8.05 (3 H, m), 7.62-7.58 (2 H, m), 7.43 (1 H, m), 7.39 (2 H, s, -$C\underline{H}_2$-), 6.97 (1 H, s, H-2' of imidazole); δ_C (50 MHz) (Me_2SO-d_6) 145.8, 138.0, 132.4, 129.8, 128.4, 124.7, 119.7, 119.5, 110.6, 56.5 (-$\underline{C}H_2$-).

N-(Benzotriazol-1-ylmethyl)-1,2,4-triazole (**4.2.7**)

Prepared (82%) (method B), as a solid, m.p. 137-138°C (prisms from ethanol) (Found: C, 54.0; H, 4.0; N, 42.0. $C_9H_8N_6$ requires: C, 54.0; H, 4.0; 42.0); δ_H (200 MHz) (Me_2SO-d_6) 9.39 (1 H, m), 8.44-8.35 (3 H, m), 7.95-7.61 (4 H, m); δ_C (50 MHz) (Me_2SO-d_6) 152.45, 145.1, 145.2, 132.3, 128.0, 124.4, 119.3, 110.6, 58.0 (-$\underline{C}H_2$-).

2-(Benzotriazol-1-ylmethyl)thiobenzothiazole (**4.2.8**)

Prepared (93%) (method B), as a solid, m.p. 116-118 °C (plates from benzene) (Found: C, 56.1; H, 3.0; N, 18.5. $C_{14}H_{10}N_4S_2$ requires: C, 56.4, 3.4, 18.8%); δ_H (200 MHz) (Me_2SO-d_6) 8.07-7.84 (4 H, m), 7.56-7.28 (4 H, m), 6.77 (2 H, s, -$C\underline{H}_2$-); δ_C (50 MHz) (Me_2SO-d_6) 162.6, 152.0, 145.2, 135.2, 132.2, 127.3, 126.1, 124.6, 124.0, 121.4, 119.1, 111.0, 48.7 (-$\underline{C}H_2$-).

4.4.2 General Procedure for Lithiation of Adducts (**4.2**) and Reaction with Electrophile Reaction with n-Butyllithium

A solution of the corresponding N-(1-benzotriazol-1-ylmethyl) heterocycle (4 mmol) in dry THF (100 ml) in a Schlenk type reactor, under argon atmosphere, was cooled to -78°C in a dry ice - acetone bath. n-Butyllithium (1.63 ml of 2.5 M solution in hexanes, 4.8 mmol) was added dropwise, very slowly. The mixture developed an intense dark color. It was kept at this temperature for 1 hour and then the corresponding electrophile (5 mmol) was added slowly (neat or in the case of benzophenone in 2 ml of THF). After the addition was complete, the color of the solution faded to light brown. The solution was allowed to warm up to room temperature over a period of 12 hours. Then a

saturated solution of NH_4Cl (100 ml) was added with vigorous stirring followed by water (25 ml) to dissolve the solid formed (LiCl). The organic material was extracted with diethyl ether (3 x 150 ml). The organic layer was washed with water (150 ml) and dried over magnesium sulfate (30 g). Removal of the solvent under vacuum (25°C/25 mmHg) yielded the crude products which were either purified by column chromatography or precipitated with a mixture of petroleum ether and diethyl ether, and then recrystallized from the appropriate solvent.

Reaction with Lithium Diisopropylamide

The procedure was the same except that instead of n-butyllithium, lithium diisopropylamide was added to the solution of (**4.2**). LDA was prepared in the following way: freshly distilled, dry diisopropylamine (4.8 mmol) was dissolved in 12 ml of dry THF and the solution was cooled to 0°C. Then n-butyllithium (1.63 ml of 2.5 M solution in hexanes, 4.8 mmol) was added dropwise. After 20 minutes the solution was transferred *via* syringe to the solution of (**4.2**).

(Benzotriazol-1-yl)(indol-1-yl)(benzoyl)methane (**4.2.1.1**)

Prepared (81%) from (**4.2.1**) using n-BuLi and ethyl benzoate, as a solid, m.p. 191-193°C (prisms petroleum ether-diethyl ether) (Found: C, 74.6; H, 4.6; N, 15.9. $C_{22}H_{16}N_4O$ requires: C, 75.0; H, 4.6; N, 15.9%); δ_H (200 MHz) (Me_2SO-d_6) 9.40 (1 H, s), 8.0-7.93 (4 H, m), 7.92-7.34 (10 H, m), 6.54 (1 H, d, J = 3 Hz, H-3' of indole); δ_C (50 MHz) (Me_2SO-d_6) 188.9 (C=O), 145.1, 135.7, 134.1, 133.5, 132.3, 28.6, 128.4, 128.0, 127.4, 124.3, 122.3, 120.7, 120.6, 119.3, 110.6, 110.3, 104.0 (C-3' of indole), 69.9 (-CH-CO).

(Benzotriazol-1-yl)(indol-1-yl)(isobutyryl)methane (**4.2.1.2**)

Prepared (95%) from (**4.2.1**) using n-BuLi and ethyl isobutyrate, as a solid, m.p. 138-140°C (needles from petroleum ether-diethyl ether) (Found: C, 71.3; H, 5.7; N, 17.4.

$C_{19}H_{18}N_4O$ requires: C, 71.7; H, 5.7; N, 17.6%); δ_H (300 MHz) ($CDCl_3$) 8.01 (1 H, d, J = 8 Hz), 7.96 (1 H, s), 7.61 (1 H, d, J = 8 Hz), 7.54 (1 H, d, J = 8 Hz), 7.37-7.14 (6 H, m), 6.65 (1 H, d, J = 3.5 Hz, H-3' of indole), 2.93 (1 H, q, J = 7 Hz, -CH-), 1.22 (3 H, d, J = 2 Hz, -CH_3), 1.20 (3 H, d, J = 2 Hz, -CH_3); δ_C (75 MHz) ($CDCl_3$) 202.9 (C=O), 146.3, 136.2, 132.2, 128.9, 128.3, 125.7, 124.4, 123.2, 121.5, 121.3, 120.2, 110.3, 109.0, 105.2 (C-3' of indole), 70.7 (-CH-CO), 38.8, 18.5, 18.0.

(Benzotriazol-1-yl)(indol-1-yl)(butyryl)methane (**4.2.1.3**)

Prepared (75%) from (**4.2.1**) using n-BuLi and ethyl butyrate, as a solid, m.p. 144-146°C (prisms from ethanol) (Found: C, 71.9; H, 5.7; N, 18.0. $C_{19}H_{18}N_4O$ requires: C, 71.7; H, 5.7; N, 17.6%); δ_H (200 MHz) (Me_2SO-d_6) 8.46-8.42 (1 H, m), 7.99 (1 H, d, J = 8 Hz), 7.89-7.77 (2 H, m), 7.56-7.06 (6 H, m), 6.56 (1 H, d, J = 3 Hz, H-3' of indole), 2.60 (2 H, t, J = 7 Hz, -CH_2-), 1.66 (2 H, q, J = 7 Hz, -CH_2-), 0.87 (3 H, t, J = 7 Hz, -CH_3); δ_C (50 MHz) (Me_2SO-d_6) 199.2 (C=O), 144.9, 135.8, 132.5, 128.0, 127.8, 127.7, 124.0, 122.0, 120.5, 120.3, 119.2, 109.9, 109.8, 103.8 (C-3' of indole), 71.3 (-CH-CO), 40.5, 13.1.

1-(p-Methylphenyl)-2-(benzotriazol-1-yl)-2-(indol-1-yl)ethanol (**4.2.1.4**)

Prepared (68%) from (**4.2.1**) using LDA and p-methylbenzaldehyde, as a solid, m.p. 224-226°C (needles from petroleum ether-diethyl ether) (Found: C, 74.6; H, 5.5; N, 15.5. $C_{23}H_{20}N_4O$ requires: C, 75.0; H, 5.5; N, 15.2%); δ_H (200 MHz) Me_2SO-d_6) 8.28 (1 H, d, J = 8.5 Hz), 7.99-7.95 (2 H, m), 7.81 (1 H, d, J = 9 Hz), 7.57-7.46 (4 H, m), 7.38-7.32 (2 H, m), 7.07-6.93 (4 H, m, protons of the phenyl ring), 6.39 (1 H, d, J = 3 Hz, H-3' of indole), 6.37-6.17 (2 H, m, CH-CH-), 2.17 (3 H, s, -CH_3); δ_C (50 MHz) (Me_2SO-d_6) 144.9, 137.6, 137.1, 135.8, 133.2, 128.6, 127.8, 127.6, 127.4, 126.8, 124.2, 121.9, 120.4, 120.1, 119.1, 111.3, 111.1, 109.9, 103.3 (C-3' of indole), 72.5 (-CH-), 71.3 (-CH-), 20.7.

N-[1-(Benzotriazol-1-yl)-2-phenylethyl]indole (**4.2.1.5**)

Prepared (86%) from (**4.2.1**) using LDA and benzyl bromide, as a solid, m.p. 107-108°C (needles from petroleum ether-diethyl ether) (Found: C, 78.3; H, 5.4; N, 16.2. $C_{22}H_{18}N_4$ requires: C, 78.1; H, 5.4; N, 16.6%); δ_H (200 MHz) ($CDCl_3$) 7.92-7.87 (1 H, m), 7.56-7.51 (1 H, m), 7.44-7.40 (2 H, m), 7.21-6.94 (11 H, m), 6.53 (1 H, d, J = 3 Hz, H-3' of indole), 4.31-3.99 (2 H, m, -C<u>H</u>$_2$-CH-); δ_C (50 MHz) ($CDCl_3$) 145.9, 135.4, 134.6, 132.0, 128.7, 128.6, 128.4, 127.6, 127.1, 124.4, 124.0, 122.4, 121.1, 120.4, 119.8, 109.1, 103.9 (C-3' of indole), 70.1 (-C<u>H</u>-), 39.4 (-C<u>H</u>$_2$-).

(Benzotriazol-1-yl)(carbazol-9-yl)(benzoyl)methane (**4.2.2.1**)

Prepared (88%) from (**4.2.2**) using n-BuLi and ethyl benzoate. The crude product was purified by column chromatography on silica gel, using benzene. Isolated as a solid, m.p. 89-91°C (plates from petroleum ether-diethyl ether) (Found: C, 77.2; H, 4.6; N, 13.6. $C_{26}H_{18}N_4O$ requires: C, 77.6; H, 4.5; N, 13.9%); δ_H (200 MHz) ($CDCl_3$) 8.77 (1 H, s), 8.01-7.85 (3 H, m) 7.80 (2 H, d, J = 8 Hz), 7.62 (2 H, d, J = 8 Hz), 7.45-7.18 (10 H, m); δ_C (50 MHz) ($CDCl_3$) 187.5 (C=O), 146.2, 139.3, 134.8, 135.0, 133.5, 129.1, 128.6, 128.4, 128.2, 126.8, 124.2, 121.3, 120.6, 120.2, 110.5, 110.1, 71.3 (-C<u>H</u>-CO).

(Benzotriazol-1-yl)(carbazol-9-yl)(butyryl)methane (**4.2.2.2**)

Prepared (84%) from (**4.2.2**) using n-BuLi and ethyl butyrate, as a solid, m.p. 189-192°C (prisms from ethanol-acetone) (Found: C, 75.0; H, 5.6; N, 15.2. $C_{23}H_{20}N_4O$ requires: C, 75.0; H, 5.5; N, 15.2%); δ_H (200 MHz) (Me_2SO-d_6) 8.68 (1 H, s), 8.08-7.50 (5 H, m), 7.43-7.27 (1 H, m), 7.25-7.22 (6 H, m), 2.87-2.46 (2 H, m, -C<u>H</u>$_2$-), 1.77-1.57 (2 H, m, -C<u>H</u>$_2$-), 0.86 (3 H, t, J = 7 Hz, -C<u>H</u>$_3$); δ_C (75 MHz) (Me_2SO-d_6) 198.3 (C=O), 143.3, 137.9, 131.7, 126.4, 124.6, 124.5, 122.7, 121.8, 119.1, 118.7, 117.9, 109.2, 108.7, 69.4 (-C<u>H</u>-CO), 39.2, 14.9, 11.8.

(Benzotriazol-1-yl)(carbazol-9-yl)(propionyl)methane (**4.2.2.3**)

Prepared (68%) from (**4.2.2**) using n-BuLi and methyl propionate, as a solid, m.p. 176-178°C (needles from ethanol) (Found: C, 74.7; H, 5.2; N, 15.7. $C_{22}H_{18}N_4O$ requires: C, 74.6; H, 5.1; N, 15.8%); δ_H (300 MHz) (Me_2SO-d_6) 7.97 (1 H, s), 7.45-7.35 (3 H, m), 7.25-7.16 (3 H, m), 6.86-6.70 (3 H, m), 6.67-6.60 (3 H, m), 2.23-1.93 (2 H, m, -C$\underline{H}_2$-), 0.50 (3 H, t, J = 7 Hz, -C$\underline{H}_3$); δ_C (75 MHz) (Me_2SO-d_6) 199.5 (C=O), 143.8, 138.3, 132.2, 126.9, 125.0, 123.2, 122.4, 119.6, 119.0, 118.3, 109.4, 109.0, 69.9 (-$\underline{C}$H-CO), 31.5, 6.3.

1-(Benzotriazol-1-yl)-1-(carbazol-9-yl)-2-pentanol (**4.2.2.4a**) and (**4.2.2.4b**)

Obtained as a mixture of two diastereoisomers from (**4.2.2.2**) using n-BuLi and n-butyraldehyde, which were separated by column chromatography on silica gel using chloroform.

(**4.2.2.4a**) Prepared (66%), as a solid, m.p. 177-179°C (leaflets from ethanol) (Found: C, 74.7; H, 6.0; N, 15.2. $C_{23}H_{22}N_4O$ requires: C, 74.6; H, 6.0; N, 15.2%); δ_H (200 MHz) ($CDCl_3$) 7.97 (1 H, d, J = 8 Hz), 7.92-7.87 (2 H, d, J = 8 Hz), 7.36-7.23 (2 H, m), 7.22-7.14 (4 H, m), 6.99-6.94 (1 H, m), 6.88 (1 H, d, J = 3 Hz), 5.65-5.59 (1 H, m, -C$\underline{H}$-OH), 3.13 (1 H, d, J = 5 Hz, -C$\underline{H}$-), 1.68-1.59 (4 H, m, 2 -C$\underline{H}_2$-), 0.92 (3 H, t, J = 7 Hz, -C$\underline{H}_3$); δ_C (50 MHz) ($CDCl_3$) 145.4, 139.6, 133.2, 128.2, 126.3, 124.5, 123.7, 120.4, 120.3, 119.95, 109.2, 71.5 (-$\underline{C}$H-OH), 70.0 (-$\underline{C}$H-), 35.4 (-$\underline{C}H_2$-), 18.7 (-$\underline{C}H_2$-), 13.8 (-$\underline{C}H_3$).

(**4.2.2.4b**) Prepared (8%), as a solid, m.p. 198-200°C (needles from ethanol) (Found: C, 74.4; H, 6.0; N, 15.1. $C_{23}H_{22}N_4O$ requires: C, 74.6; H, 6.0; N, 15.2%); δ_H (200 MHz) ($CDCl_3$) 8.03 (2 H, d, J = 8 Hz), 7.94 (1 H, d, J = 9 Hz), 7.62 (2 H, d, J = 8 Hz), 7.40 (2 H, t, J = 7 Hz), 7.27-6.99 (6 H, m), 5.91-5.85 (1 H, m, -C$\underline{H}$-OH), 4.41 (1 H, d, J = 4 Hz, -C$\underline{H}$-), 1.62-1.05 (4 H, m, 2 -C$\underline{H}_2$-), 0.71 (3 H, t, J = 7 Hz, -C$\underline{H}_3$); δ_C (50 MHz)

($CDCl_3$) 145.7, 133.3, 128.2, 126.5, 124.5, 123.6, 120.5, 119.8, 109.5, 72.8 (-CH-OH), 69.0 (-CH-), 33.7 (-CH_2-), 18.4 (-CH_2-), 13.5 (-CH_3).

N-[(Benzotriazol-1-yl)methyl]-2-benzoylbenzimidazole (**4.2.3.1**)

Prepared (78%) from (**4.2.3**) using n-BuLi and ethyl benzoate, as a solid, m.p. 137-139°C (microcrystals from petroleum ether - diethyl ether) (Found: C, 71.2; H, 4.3; N, 19.8. $C_{21}H_{15}N_5O$ requires: C, 71.4; H, 4.3; N, 19.8%); δ_H (200 MHz) ($CDCl_3$) 8.39-8.34 (2 H, m), 8.07-7.95 (2 H, m), 7.89-7.60 (2 H, m), 7.56-7.25 (9 H, m); δ_C (50 MHz) ($CDCl_3$) 186.9 (C=O), 145.9, 144.8, 141.7, 136.4, 135.4, 133.9, 132.2, 131.3, 128.3, 127.1, 124.6, 124.3, 122.1, 119.9, 112.1, 110.0, 55.5 (-CH-CO).

N-[(Benzotriazol-1-yl)methyl-α-benzyl]-2-phenylbenzimidazole (**4.2.5.1**)

Prepared (83%) from (**4.2.5**) using n-BuLi and benzyl bromide, as a solid, m.p. 176-178°C (needles from petroleum ether-diethyl ether) (Found: C, 78.1; H, 5.4; N, 16.5. $C_{27}H_{21}N_5$ requires: C, 78.1; H, 5.1; N, 16.9%); δ_H (200 MHz) ($CDCl_3$) 8.39-8.10 (2 H, m), 7.86-7.79 (1 H, m), 7.69-7.07 (15 H, m), 6.81-6.65 (1 H, m, -CH-), 4.90-4.51 (2 H, m, -CH_2-Ph); δ_C (50 MHz) ($CDCl_3$) 153.4 (C-2' of benzimidazole), 145.6, 143.2, 134.6, 132.5, 132.2, 130.2, 129.8, 129.3, 128.9, 128.7, 127.8, 127.7, 124.3, 123.7, 123.2, 120.2, 120.0, 112.7, 108.8, 69.8 (-CH-), 38.1 (-CH_2-).

N-[(Benzotriazol-1-yl)methyl-α-(diphenylhydroxymethyl)]-2-phenylbenzimidazole (**4.2.5.2**)

Prepared (79%) from (**4.2.5**) using n-BuLi and benzophenone, as a solid, m.p. 159-162°C (prisms from acetone) (Found: C, 78.1; H, 4.9; N, 13.9. $C_{33}H_{25}N_5O$ requires: C, 78.1; H, 5.0; N, 13.8%); δ_H (300 MHz) ($CDCl_3$) 7.96 (2 H, m), 7.84-7.83 (1 H, m), 7.71-7.70 (1 H, m), 7.51-6.88 (20 H, m), 6.12 (1 H, s, -CH-); δ_C (75 MHz) ($CDCl_3$) 153.9 (C-2' of benzimidazole), 144.6, 143.7, 143.1, 143.0, 142.9, 140.7, 133.7, 132.9, 132.3,

130.2, 129.8, 128.9, 128.6, 128.5, 127.8, 127.5, 125.2, 124.8, 123.6, 120.5, 119.8, 114.9, 109.0, 83.4 [-C(OH)Ph_2], 73.0 (-CH-).

[(Benzotriazol-1-yl)-(imidazol-1-yl)-benzoyl]methane (**4.2.6.1**)

Prepared (53%) from (**4.2.6**) using n-BuLi and ethyl benzoate, as a solid, m.p. 58-62°C (needles from diethyl ether-acetone) (Found: C, 67.0; H, 4.4; N, 23.0. $C_{17}H_{13}N_5O$ requires: C, 67.3; H, 4.3; N, 23.1%); δ_H (200 MHz) ($CDCl_3$) 8.66 (1 H, s), 8.09 (1 H, d, J = 8 Hz), 7.90-7.86 (2 H, m), 7.57-7.22 (8 H, m), 7.02 (1 H, m); δ_C (50 MHz) ($CDCl_3$) 186.6 (C=O), 146.2 (C-3a), 137.0, 134.9, 132.8, 131.7, 129.9, 129.1, 128.6, 125.0, 120.5, 119.0, 109.5, 69.6 (-CH-).

N-[(Benzotriazol-1-yl)methyl]-2-benzoylimidazole (**4.2.6.2**)

Prepared (30%) from (**4.2.6**) using n-BuLi and ethyl benzoate, in the same reaction as (**4.2.6.1**), (isolated from the reaction mixture by column chromatography as the less polar fraction), as solid, m.p. 113-114°C (prisms from ethanol) (Found: C, 67.7; H, 4.3; N, 23.4. $C_{17}H_{13}N_5O$ requires: C, 67.3; H, 4.3; N, 23.1%); δ_H (200 MHz) ($CDCl_3$) 8.33-8.28 (2 H, m), 8.07-8.02 (1 H, m), 7.91-7.87 (1 H, m), 7.60-7.32 (8 H, m), 7.23 (1 H, s); δ_C (50 MHz) ($CDCl_3$) 184.8 (C=O), 145.8 (C-3a), 141.7, 136.6, 133.2, 132.1, 130.9, 130.6, 128.5, 128.1, 125.2, 124.5, 119.9, 109.9, 56.9 (-CH_2-).

N-[(Benzotriazol-1-yl)methyl]-2-[(4-methylphenyl)-1-hydroxymethyl]imidazole (**4.2.6.3**)

Prepared (74%) from (**4.2.6.**) using n-BuLi and p-methylbenzaldehyde, as a solid, m.p. 89-91°C (prisms from diethyl ether-acetone) (Found: C, 67.4; H, 5.3; N, 22.0. $C_{18}H_{17}N_5O$ requires: C, 67.7; H, 5.4; N, 21.9%); δ_H (200 MHz) ($CDCl_3$) 7.95-7.89 (1 H, m), 7.30-6.79 (7 H, m), 6.70-6.13 (5 H, m), 3.30 (3 H, s), 2.19 (1 H, s); δ_C($CDCl_3$) 149.2 (C-2 of imidazole), 145.7 (C-3a), 137.6, 137.4, 132.1, 129.5, 127.9, 127.2, 125.5, 124.3, 119.9, 119.6, 109.7, 68.7 (-CH-OH), 56.3 (-CH_2-), 21.0 (-CH_3).

N-(Benzoylmethyl)indole (**4.3**)

The benzotriazole adduct (0.352 g, 1 mmol) was dissolved in a mixture of ethanol (15 ml) and THF (10 ml) and acetic acid (2 ml). Then freshly prepared powdered zinc (0.33 g, 10 mmol) was added in one portion. The suspension was kept under nitrogen on the ultrasonic bath for 10 hours. Since there was still starting material present as monitored by TLC, 0.33 g of Zn and three drops of HCl concentrated was added and the mixture was stirred at room temperature for an additional 24 hours. After the reaction went to completion (TLC), the suspension was diluted with 20 ml of EtOH and 10 ml of THF and filtered through celite 545. The filtrate was concentrated to about 1/4 its volume and 15 ml of H_2O was added followed by solid sodium bicarbonate until a neutral pH was attained. The organic material was then extracted with chloroform (3 x 40 ml). The organic layer was washed with water (30 ml) and dried ($MgSO_4$). Evaporation of the solvent yielded a solid (43% yield) which was recrystallized from ethanol. M.p. 134-135.5°C (needles) (Found: C, 82.0; H, 5.6; N, 6.0. $C_{16}H_{13}NO$ requires: C, 81.7; H, 5.6; N, 6.0); δ_H (200 MHz) (Me_2SO-d_6) 8.01-7.97 (2 H, m), 7.64-7.51 (4 H, m), 7.15-7.06 (4 H, m), 6.53 (1 H, d, J = 3 Hz, H-3 of indole), 5.56 (2 H, s, -CH_2-); δ_C (50 MHz) (Me_2SO-d_6) 192.5 (C=O), 135.7, 133.7, 133.0, 128.2, 128.0, 127.1, 120.7, 119.9, 118.6, 108.3, 100.9, 51.4 (-CH_2-CO).

4.4.3 General Procedure for the Reduction of Acyl and Benzoyl Adducts of Indole and Carbazole with $NaBH_4$

The acyl or benzoyl adduct of indole or carbazole (2 mmol) was dissolved in ethanol (25 ml) and THF (2 ml). Sodium borohydride (4 mmol) was then added in one portion. The reaction was monitored by TLC. After 5 minutes there was no starting material left. The solution was treated with 10 ml of water, the mixture concentrated to about 1/2 its volume and the organic material extracted with $CHCl_3$ (3 x 25 ml). The

organic layer was then washed with water (20 ml), dried ($MgSO_4$), and the solvent removed under vacuum to give the crude products which were purified accordingly.

1-Phenyl-2-(benzotriazol-1-yl)-2-(indol-1-yl)ethanol (**4.2.1.6**)

Prepared (95%) from (**4.2.1.1**) by reduction with $NaBH_4$ as a mixture of two diastereoisomers in (9 : 4) ratio. Solid recrystallized from ethanol with broad melting point 200-222°C (Found: C, 74.6; H, 5.1; N, 15.9. $C_{22}H_{18}N_4O$ requires: C, 74.6; H, 5.1; N, 15.8%); δ_H (200 MHz) ($CDCl_3$) 7.93-7.89 (2 H, m), 7.59-7.54 (4 H, m), 7.31-6.86 (24 H, m), 6.43 (1 H, d, J = 4 Hz), 6.27 (1 H, d, J = 3 Hz), 6.26-6.24 (2 H, m), 4.17 [1 H, d, J = 4 Hz, -CH-OH], 3.94 [1 H, d, J = 3.5 Hz, -CH-OH]; δ_C (50 MHz) ($CDCl_3$) 145.2, 145.0, 137.9, 137.8, 136.6, 135.5, 128.6, 128.5, 128.4, 128.3, 128.0, 126.3, 126.2, 125.8, 125.0, 124.7, 124.2, 122.5, 121.2, 121.1, 120.5, 120.3, 119.7, 109.6, 109.2, 108.8, 108.7, 104.4, 74.3, 73.9, 73.5, 72.1.

3-Methyl-1-(benzotriazol-1-yl)-1-(indol-1-yl)-2-butanol (**4.2.1.7a**) and (**4.2.1.7b**)

Obtained (87%) as a mixture of two diastereoisomers (ratio 7 : 4) from (**4.2.1.2**). They were separated based on their differing solubility in diethyl ether.

(4.2.1.7a) The compound soluble in diethyl ether was obtained as a solid (56% of the theoretical yield), m.p. 83-85°C (leaflets from ethanol)(Found: M^+, 320.1641, calculated for $C_{19}H_{20}N_4O$: M^+, 320.1637); δ_H (200 MHz) ($CDCl_3$) 7.84-7.75 (2 H, m), 7.59-7.42 (2 H, m), 7.29-7.07 (5 H, m), 6.55 (1 H, d, J = 4 Hz, H-3 of indole), 4.89-4.87 (1 H, m, -CH-OH), 3.97 (1 H, d, J = 4 Hz, -CH-), 2.06 (1 H, s), 2.03-1.70 (1 H, m, -CH- of isopropyl), 1.03 (6 H, d, J = 7 Hz, $-CH_3$); δ_C (50 MHz) ($CDCl_3$) 145.3 (C-3a), 136.5, 123.4, 128.3, 128.0, 127.9, 124.3, 121.2, 120.6, 119.6, 109.7, 108.9, 104.2, 76.6 (-CH-OH), 69.5 (-CH-), 29.8 (-CH-), 19.8 ($-CH_3$), 16.8 ($-CH_3$).

(4.2.1.7b) The compound insoluble in diethyl ether was obtained as a solid (31% of the theoretical yield), m.p. 201-203°C (prisms from ethanol) (Found: C, 70.8 H, 6.3; N,

17.3. $C_{19}H_{20}N_4O$ requires: C, 71.2; H, 6.3; N, 17.5%); δ_H (200 MHz) (Me_2SO-d_6) 8.10 (1 H, d, J = 8 Hz), 7.85-7.70 (3 H, m), 7.31 (2 H, d, J = 7 Hz), 7.26-6.79 (3 H, m), 6.36 (1 H, d, J = 3 Hz, H-3 of indole), 5.35-5.32 (1 H, m, -CH-OH), 5.00-4.96 (1 H, m, -CH-), 3.21 (1 H, s), 1.33-1.29 (1 H, -CH-), 0.82-0.71 (6 H, m, 2 -CH_3); δ_C (50 MHz) (Me_2SO-d_6) 145.0 (C-3a), 135.6, 133.1, 128.1, 127.5, 126.7, 124.2, 122.3, 120.7, 120.3, 119.1, 111.2, 110.0, 103.6, 73.2 (-CH-OH), 70.1 (-CH-), 29.1 (-CH-), 20.1 (-CH_3), 14.9 (-CH_3).

1-(Benzotriazol-1-yl)-1-(indol-1-yl)-2-pentanol (**4.2.1.8a**) and (**4.2.1.8b**)

Prepared (82%) from (**4.2.1.3**) as a mixture of two diastereoisomers that were partially separated by column chromatography on silica gel using $CHCl_3$.

(4.2.1.8a) Prepared (45%) (calculated as a total yield of both pure isomer and from the unseparated mixture) as a solid m.p. 79-80°C (prisms from ethanol) (Found: M^+, 320.1659, calculated for $C_{19}H_{20}N_4O$: M^+, 320.1637); δ_H (200 MHz) ($CDCl_3$) 7.93-7.89 (1 H, d, J = 9 Hz), 7.62-7.36 (3 H, m), 7.33-7.10 (5 H, m), 6.77 (1 H, d, J = 8 Hz), 6.67 (1 H, d, J = 3 Hz, H-3 of indole), 5.06 (1 H, m, -CH-OH), 3.76 (1 H, d, J = 4 Hz, -CH-), 1.72-1.26 (4 H, m, 2 -CH_2-), 0.86 (3 H, t, J = 7 Hz, -CH_3); δ_C (50 MHz) ($CDCl_3$) 145.7 (C-3a), 135.8, 133.2, 128.6, 128.3, 124.8, 124.6, 122.9, 121.5, 120.7, 119.8, 109.6, 108.9, 104.7, 72.6 (-CH-OH), 71.4 (-CH-), 34.4 (-CH_2-), 18.5 (-CH_2-), 13.7 (-CH_3).

(4.2.1.8b) Prepared (37%) (calculated as a total yield of both pure isomer and from the unseparated mixture) as a solid m.p. 156-158°C (prisms from ethanol) (Found: C, 71.2; H, 6.3; N, 17.5. $C_{19}H_{20}N_4O$ requires: C, 71.2; H, 6.3; N, 17.5%); δ_H (200 MHz) ($CDCl_3$) 7.91 (1 H, d, J = 9 Hz), 7.62 (2 H, m), 7.27-7.05 (5 H, m), 6.84 (1 H, d, J = 5 Hz), 6.55 (1 H, d, J = 3 Hz, H-3 of indole), 5.15 (1 H, m, -CH-OH), 3.78 (1 H, d, J = 6 Hz, -CH-), 1.64-1.43 (5 H, m, 2 -CH_2-), 0.91 (3 H, t, J = 7 Hz, -CH_3); δ_C (50 MHz) ($CDCl_3$) 145.4 (C-3a), 136.6, 132.6, 128.4, 128.3, 126.0, 124.5, 122.6, 121.4, 120.6, 119.8, 109.6, 108.7, 104.3, 71.9 (-CH-OH), 71.1 (-CH-), 34.6 (-CH_2), 18.7 (-CH_2-), 13.7 (-CH_3).

1-(Benzotriazol-1-yl)-1-(carbazol-1-yl)-2-pentanol (**4.2.2.4**)

Prepared (99%) from (**4.2.2.2**) by reduction with $NaBH_4$ predominantly as one diastereoisomer. Recrystallized from ethanol m.p. 176-178°C (prisms) (Found: C, 74.4; H, 6.0; N, 15.3. $C_{23}H_{22}N_4O$ requires: C, 74.6; H, 6.0; N, 15.2%); δ_H(200 MHz) ($CDCl_3$) 8.03-7.96 (3 H, m), 7.67-7.63 (1 H, m), 7.23-6.88 (10 H, m), 5.63 (1 H, m, -C<u>H</u>-OH), 3.18 (1 H, s, -C<u>H</u>-), 1.74-1.42 (4 H, m, 2 -C<u>H</u>$_2$-), 0.95-0.83 (3 H, m, -C<u>H</u>$_3$); δ_C (50 MHz) ($CDCl_3$) 145.3 (C-3a), 139.2, 133.1, 128.2, 126.4, 124.5, 124.2, 120.5, 120.4, 120.3, 119.9, 119.8, 109.5, 109.1, 71.5 (-<u>C</u>H-OH), 70.0 (-<u>C</u>H-), 35.4 (-<u>C</u>H$_2$-), 18.7 (-<u>C</u>H$_2$-), 13.8 (-<u>C</u>H$_3$).

CHAPTER V
REACTIVITY OF 1-TRIMETHYLSILYLBENZOTRIAZOLE

5.1 Introduction

5.1.1 Physical Properties of Silicon

Silicon's utility in organic synthesis depends upon several factors: (i) its relatively low electronegativity, (ii) the strength of its bonds to other elements, and (iii) the involvement of its valence p- and empty d-orbitals. Relative electronegativity can be established on several empirical scales. Regardless of the scale used, silicon always appears to be more electropositive than carbon. As a result, there is a strong polarization of the carbon-silicon bond and a tendency for nucleophilic attack on silicon. From bond dissociation energies [81MI4], it can be seen that silicon bonds to oxygen and fluorine are significantly stronger than silicon bonds to hydrogen or carbon. By contrast, the value for the dissociation energy of the N-Si bond is approximately the same as that of C-Si.

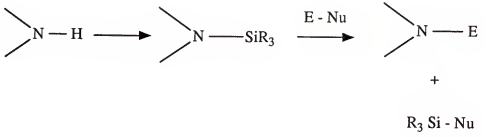
5.1.2 Silylation of Organic Compounds

The replacement of protons attached to heteroatoms by trialkylsilyl groups (most often trimethylsilyl - TMS), usually changes the reactivity of a molecule either at the site of the newly introduced substituent or in the adjacent positions of the molecule. The trialkylsilyl substituent often serves as a protecting group for sensitive functional groups. Many trimethylsilyl based reagents, for example: halogenosilanes [68JOM(15)57, 75LA266, 76ACS(B)574], alkylthiosilanes [60JCS4406, 61JCS4933], phenylselenosilane [78TL5087, 78TL5091, 79TL4189], and azidosilane [71JOM(33)153], have proved to be

of synthetic utility. Amino- and amido-silanes are the most reactive class of organosilanes in which silicon is bonded to a more electronegative element [70ACR(3)299, 72MI97].

5.1.3 Reactivity of the Nitrogen-Silicon Bond

The nitrogen-silicon bond is formed readily by a variety of methods. Hexamethyldisilazane (HMDS) [68JHC(5)785] and trimethylsilyl chloride (TMS-Cl) [62JOC(27)2190] in nonpolar solvents such as toluene or benzene, are the most common silylating agents. Although the silicon-nitrogen bond is quite labile under aqueous conditions, the TMS moiety can be a useful protecting group for the amino functionality when anhydrous conditions are employed [76S40, 76JOM(121)25]. Such protection can withstand a variety of hindered nucleophiles [68AG(E)(7)809] and the silicon-nitrogen bond can be cleaved under mild electrophilic conditions (Scheme 5.1).

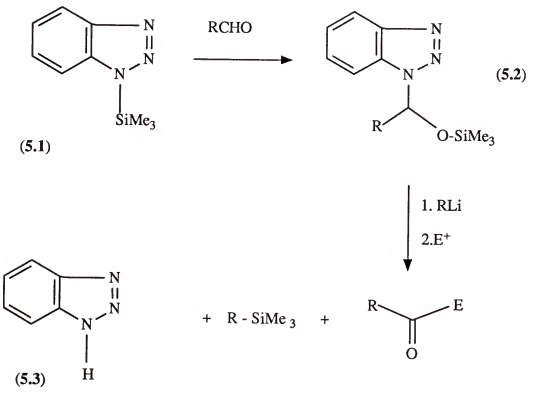


Scheme 5.1

The reactivity of organosilylamine derivatives of imidazole, pyrazole, 1,2,4-triazole and benzotriazole toward alkyl halides, acid chlorides, aldehydes and halogenated ketones, has been studied previously [80JOM(188)141]. The corresponding N-substituted products were obtained in good yields [60CB(93)2804, 77JOM(133)169]. Aldehydes reacted easily with organosilicon amines giving addition products. These reactions were carried out on an NMR scale and the products (presumably unstable) were not isolated.

5.1.4 Aim of the Work

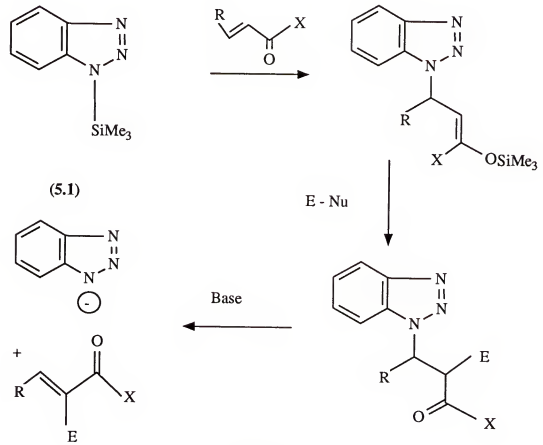
Our interest was focused on the reactivity of compounds where the trimethylsilyl group was bonded to a nitrogen atom that was part of a heterocyclic ring. The goal was to examine the reactivity of 1-trimethylsilylbenzotriazole (**5.1**) towards aldehydes, its ability to transfer the TMS group from nitrogen to oxygen, and the use of the trimethylsilyl moiety as a protecting/activating group on oxygen during the lithiation reaction (Scheme 5.2). The electron-withdrawing character of the benzotriazole ring should increase the acidity of the alpha protons and facilitate proton abstraction. Thus, the proposed overall scheme would be an example of umpolung. The normally electrophilic carbon of an



Scheme 5.2

aldehyde would be made to behave as a nucleophile and the adduct (**5.2**) would serve as a masked form of an acyl anion.

In addition, the reactions of (**5.1**) with α,β-unsaturated carbonyl compounds could give a new way of carbon-nitrogen bond formation. This could also provide a useful intermediate that could be, in turn, susceptible to electrophilic addition (Scheme 5.3). Finally, the benzotriazole moiety, which would have served as a masking group for a double bond in the case of 1,4-addition, could be eliminated to give α-substituted-α,β-unsaturated carbonyl compounds.

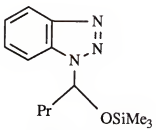


Scheme 5.3

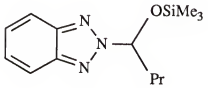
5.2 Results and Discussion

5.2.1 Reaction of 1-Trimethylsilylbenzotriazole with Aliphatic and Aromatic Aldehydes

The starting material, 1-trimethylsilylbenzotriazole (**5.1**), was easily prepared according to the literature procedure [68JHC(5)785] using hexamethyldisilazane and a catalytic amount of ammonium sulfate under anhydrous conditions. The product was extremely susceptible to hydrolysis and had to be stored in a moisture free atmosphere. The reaction of butyraldehyde with 1-trimethylsilylbenzotriazole gave a mixture of two isomers (Figure 5.2).



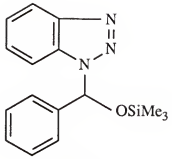
(5.4a)



(5.4b)

Figure 5.2

This mixture was characterized by ^{1}H and ^{13}C NMR. Thus the characteristic α-protons for both isomers appeared in the region 6.65-6.15 ppm. By integration, about 30% of the mixture was the 2-isomer (**5.4b**). In the ^{13}C NMR spectrum of the mixture, nine aromatic carbons could be distinguished that corresponded to the 1- and 2-substituted benzotriazoles [83H(20)1787]. The carbon attached to the heterocyclic nitrogen appeared at δ 88.3 and δ 84.1 ppm for the 1- and 2-isomers respectively. The reaction of benzaldehyde with 1-trimethylsilylbenzotriazole proceeded in a quantitative yield



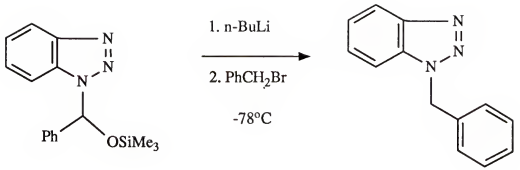
(**5.5**)

Figure 5.3

at room temperature to give only one product (Figure 5.3). The structure of compound (**5.5**) was confirmed by comparison of its spectral data with literature values [81JOM(208)309].

5.2.2 Attempts at Lithiation and Addition of Electrophiles to (**5.5**)

Deprotonation of (**5.5**) with n-butyllithium in hexanes at -78°C followed by addition of benzyl bromide resulted in formation of N-benzylbenzotriazole (**5.6**) as the major isolated product (Scheme 5.4). Formation of this product could be explained by the following mechanism: n-BuLi attacked the silicon to free benzaldehyde and benzotriazolyl anion. The latter reacted directly with benzyl bromide to give (**5.6**). In order to avoid this path a more hindered base, lithium diisopropylamide, was used. Deprotonation was followed by addition of different electrophiles. In the case of benzyl bromide 1-benzylbenzotriazole (**5.6**) was obtained. When p-methylbenzaldehyde was used as an electrophile, only a mixture of starting materials was recovered. The outcome of these reactions could be explained by the fact that the organometallic reagent was attacking silicon causing formation of the stable lithium salt of benzotriazole which in turn



(**5.5**) (**5.6**)

Scheme 5.4

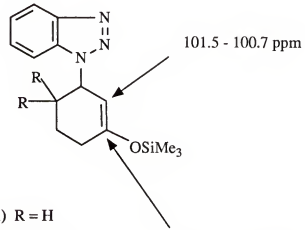
reacted with benzyl bromide. From the above results it was clear that abstraction of a proton from the α-carbon of (**5.5**) was not feasible.

5.2.3 Reaction of 1-Trimethylsilylbenzotriazole with Other Electrophiles

Other reactions of (**5.1**) were attempted with benzonitrile and simple Michael acceptors like acrylonitrile, ethyl acrylate, and benzoquinone. These reactions were carried out at room temperature and at 60°C in the absence of solvent. No positive results were obtained.

Successful results, however, were obtained with α,β-unsaturated ketones, particularly the derivatives of cyclohexenone. Reactions of 1-trimethylsilylbenzotriazole (**5.1**) with cyclohexenone, 4,4-dimethylcyclohexen-2-one, and 4-isopropylcyclohexen-2-one proceeded at room temperature under a dry nitrogen atmosphere without any solvent. The products 1-trimethylsilyloxy-3-(benzotriazol-1-yl)-1-cyclohexenes (**5.7**) were very unstable and moisture sensitive compounds. In the presence of moisture they underwent

hydrolysis to the corresponding ketones. Attempts to isolate and purify these trimethyl silyl enol ethers failed. However, it was possible to examine the spectral properties of two of them. The most indicative signals in the ^{13}C NMR spectra of all silyl enol ethers (**5.7**) appeared to be the chemical shift corresponding to the quaternary carbon attached to the trimethylsilyloxy substituent. This peak appeared in the region δ 159.0-155.0 ppm. The unsaturated carbon C-2 of the cyclohexyl ring appeared at about δ 101.5-100.7 ppm (Figure 5.4).



(**5.7.1**) R = H
(**5.7.2**) R = Me

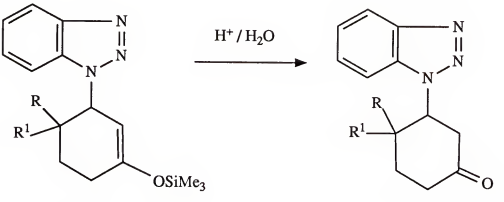
Figure 5.4

5.2.4 Reactivity of 1-Trimethylsilyloxy-3-(benzotriazol-1-yl)-1-cyclohexene (**5.7.1**) Towards Electrophiles

Electrophiles usually react stereospecifically at the carbon-carbon double bond of trimethylsilyl enol ethers. The nucleophilic anion associated with the electrophile attacks the silicon center to yield, upon hydrolysis, an α-substituted ketone [for a review see 68JA(90)4462, 4464, 69JOC(34)2324, 75PAC(43)553, 77S91].

5.2.4.1 Acid Hydrolysis

Hydrolysis of the silyl enol ethers with 1 M hydrochloric acid yielded the corresponding ketones (**5.8**) (Scheme 5.5). All the hydrolysis products were characterized by their analytical data (Table 5.1).



(**5.7**)

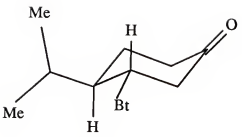
(**5.8.1**) $R = R^1 = H$

(**5.8.2**) $R = R^1 = Me$

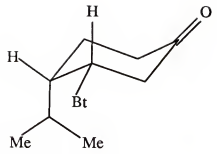
(**5.8.3**) $R = H$ $R^1 = Pr^i$

Scheme 5.5

Two isomeric compounds were isolated after purification by column chromatography of the crude hydrolysis product (**5.8.3**). Analysis of spectral and analytical data (see Experimental) for both compounds suggested that they were *cis* and *trans* geometrical isomers (Figure 5.5). Indeed, in the ^1H NMR spectrum for the *trans* isomer, the hydrogen attached to the C-3 carbon of the cyclohexyl ring appeared as a well resolved six-line signal. The signal for the analogous hydrogen in the *cis* isomer was very broad.



trans (**5.8.3**a)



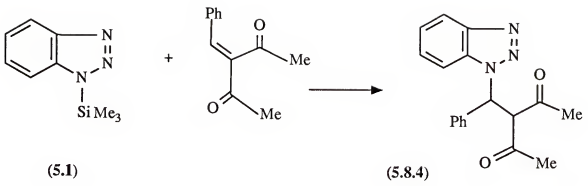
cis (**5.8.3b**)

Bt = 1-Benzotriazolyl

Figure 5.5

Table 5.1 Preparation of β-(Benzotriazol-1-yl) Ketones (**5.8**)

Product	Yield (%)	M.p. (°C)	Elemental Analysis Found (Calculated) C(%)	H(%)	N(%)
(**5.8.1**)	70	105-107	66.8(67.0)	6.2(6.1)	19.2(19.5)
(**5.8.2**)	74	106-108	68.8(69.1)	7.3(7.0)	17.0(17.3)
(**5.8.3**a)	22	104-106	70.1(70.1)	7.7(7.4)	16.2(16.3)
(**5.8.3**b)	7	-	70.0(70.1)	7.7(7.4)	16.2(16.3)
(**5.8.4**)	22	128-130	70.4(70.3)	5.8(5.6)	13.5(13.7)



(5.1) **(5.8.4)**

Scheme 5.6

The ability of benzotriazole to transfer a trimethylsilyl group was not limited only to the cyclohexenone system. Reaction of (**5.1**) with 3-(1-phenylmethylene)penta-2,4-dione in the presence of a mild Lewis acid (a catalytic amount of $ZnCl_2$) yielded, after purification by column chromatography, the corresponding ketone (**5.8.4**) in low (22%) yield. The spectral characterization of the intermediate silyl enol ether was not possible in this case (as for 4-isopropylcyclohexen-2-one) because of rapid conversion to the ketone (Scheme 5.6). All the 3-substituted ketones displayed ^{13}C NMR spectra with characteristic patterns for 1-substituted benzotriazoles. Table 5.2 shows the chemical shifts of the carbons in the benzotriazole moiety, the carbonyl carbon, and the methine carbon to which the heterocyclic nitrogen was attached. The signals obtained in the aliphatic region of the spectra for products (**5.8**) corresponded to the chemical shifts reported for substituted cyclohexanones [78MI163].

The ^1H NMR spectra of products (**5.8**) of showed a typical four proton pattern for 1-substituted benzotriazole. The H-4' proton appeared as a well resolved doublet, downfield at about δ 8.1 ppm, with a coupling constant of 8 Hz, and the remaining H-5',

H-6', and H-7' protons gave a complex multiplet. The proton attached to the carbon bonded to nitrogen was detected as a well resolved signal in the region of δ 6.5-4.9 ppm with a coupling constant in the range of 5-11 Hz. In the infrared spectra of the substituted ketones, the characteristic carbonyl stretching vibration appeared as a strong band in the region of 1740-1710 cm^{-1}.

Table 5.2 ^{13}C NMR Chemical Shifts for Benzotriazole Carbons, Carbonyl Carbon, and the Methine Carbon

Product	C=O	C-3a'	C-4'	C-5'	C-6'	C-7'	C-7a'	CH-3
(5.8.1)	206.5	145.5	119.6	123.9	127.2	109.0	131.8	56.4
(5.8.2)	206.9	145.0	119.8	123.8	127.2	109.5	133.7	63.8
(5.8.3a)	206.7	145.6	120.1	124.0	127.5	108.7	132.4	58.6
(5.8.3b)	206.5	145.0	120.1	123.9	127.4	108.9	133.6	57.4
(5.8.4)[a]	199.4	145.8	119.5	124.1	127.5	109.6	132.5	71.5

[a]This product had two nonequivalent carbonyl carbons, the chemical shift of the second carbonyl carbon was 198.7 ppm.

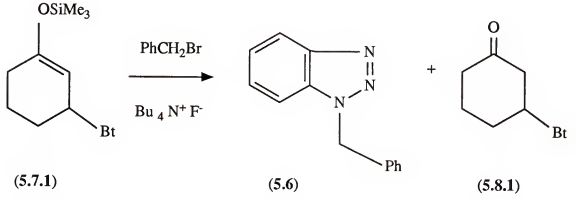
5.2.4.2 Reactions with Alkyl Halides, Halogens, Acid Chlorides, and Aldehydes

We attempted reactions of 1-trimethylsilyloxy-3-(benzotriazol-1-yl)-1-cyclohexene **(5.7.1)** with a variety of electrophiles. The most productive sets of conditions for this type of reaction included: (i) Lewis acids such as $TiCl_4$ in methylene chloride [79TL1519], and (ii) fluoride ion in the form of $Bu_4N^+F^-$ [77JA(99)1265] or KF [79JA(101)7007,

80(36)T2, 80JOC(45)1066]. The reactions with alkyl halides, for example methyl iodide and t-butyl bromide, were unsuccessful.

Reaction with Benzyl Bromide

In the reaction of benzyl bromide with silyl enol ether (**5.7.1**), only the hydrolysed product (**5.8.1**) was obtained. Formed *in situ*, the silyl enol ether was treated with benzyl bromide and an equivalent amount of tetrabutylammonium fluoride in THF under nitrogen. Two products were isolated from the reaction mixture (Scheme 5.7). Purification by column chromatography yielded 75% of 1-benzylbenzotriazole (**5.6**) and 22% of 3-(benzotriazol-1-yl)cyclohexanone (**5.8.1**). The structure of product (**5.6**) was based on spectral data, elemental analysis, and comparison of its melting points with the value reported in the literature [56JCS1076].

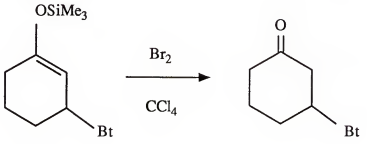


(**5.7.1**) (**5.6**) (**5.8.1**)

Scheme 5.7

Reaction with Halogens

Halogens are known to react regiospecifically with trimethylsilyl enol ethers to yield α-haloketones [76S194]. The reaction of 1-trimethylsilyloxy-3-(benzotriazol-1-yl)-1-cyclohexene (**5.7.1**) with bromine in carbon tetrachloride yielded only the corresponding ketone (**5.8.1**) (Scheme 5.8).

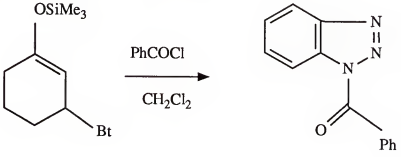


(**5.7.1**) (**5.8.1**)

Scheme 5.8

Reaction with Benzoyl Chloride

Treating silyl enol ether (**5.7.1**) with benzoyl chloride in methylene chloride under nitrogen at room temperature gave, after recrystallization from methanol, 1-benzoyl-benzotriazole (**5.9**) in 74% yield (Scheme 5.9).



(**5.7.1**) (**5.9**)

Scheme 5.9

The product (**5.9**) was identified on the basis of its analytical and spectral (^1H, ^{13}C NMR, and IR) data, as well as by comparison of its melting point with an authentic sample.

Formation of both products, 1-benzyl- (**5.6**) and 1-benzoylbenzotriazole (**5.9**), could be explained by the following mechanism. Although a halide anion (fluoride or chloride) attacked the silicon as expected, the electrophile coordinated with benzotriazole ultimately resulting in cleavage of the carbon-nitrogen bond as shown in Figure 5.6.

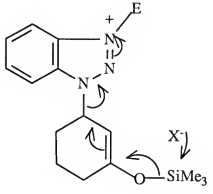
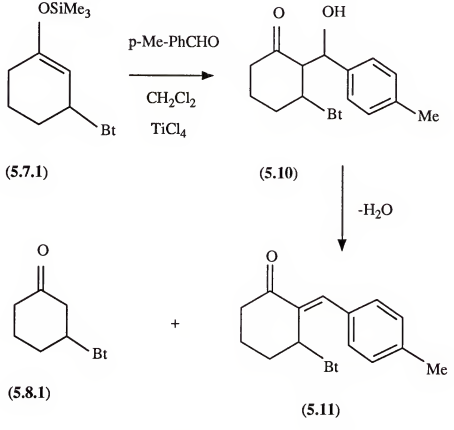


Figure 5.6

Reaction with p-Methylbenzaldehyde

Reactions of silyl enol ethers with aldehydes and ketones are facilitated by addition of $TiCl_4$ as reported by Mukaiyama and coworkers [73CL1011]. Based on this precedent a solution of the trimethylsilyl enol ether (**5.7.1**) in methylene chloride was

treated at -60°C with an equivalent amount of p-methylbenzaldehyde and titanium tetrachloride. Product (**5.11**) was isolated in addition to 3-substituted cyclohexanone (**5.8.1**) (Scheme 5.10).



Scheme 5.10

Compound (**5.11**) was the dehydration product of the corresponding aldol (**5.10**) obtained from the reaction of the silyl enol ether (**5.7.1**) at the 2-position with p-methyl-benzaldehyde. The structure of this product was based on analytical and spectral data (see Experimental).

5.3 Conclusions

Our attempts to utilize the benzotriazole moiety as a masking group for the acyl functionality were not very successful. As shown, formation of a carbanion from 1-(α-trimethylsilyloxybenzyl)benzotriazole (**5.5**) suffered from competing side reactions. The stability of the lithium salt of the benzotriazole could be the driving force for the reverse reaction. The second part of this chapter dealt with the reactivity of 1-trimethylsilyloxy-3-(1-benzotriazol-1-yl)-1-cyclohexene (**5.7.1**) towards electrophiles. The present work showed that this silyl enol ether was not very susceptible towards electrophiles. More reactive electrophiles attacked elsewhere in the molecule at the heterocyclic nitrogen. Steric hindrance at the carbon-carbon double bond in comparison with the easy access to nitrogen could account for this result. The reaction with p-methylbenzaldehyde, although it led to the elimination product (**5.11**), went through the desired reaction path.

5.4 Experimental

General procedures and apparatus used in this Chapter are identical as those described in Chapter IV. Additionally, ^{1}H NMR spectra were obtained on a Varian EM 360L (60 MHz, continuous wave mode) spectrometer, if unspecified, or Varian XL200 (200 MHz, FT mode) spectrometer, as specified, with tetramethylsilane as an internal standard. ^{13}C NMR spectra were run on a Jeol JNM-FX 100 (25 MHz, FT mode) spectrometer, if unspecified, or Varian XL200 (50 MHz, FT mode) spectrometer, referring to the center signal of $CDCl_3$ (77.0 ppm) or Me_2SO-d_6 (39.5 ppm) respectively.

1-Trimethylsilylbenzotriazole (**5.1**) was prepared according to the literature procedure, b.p. 85°C/0.7 mmHg {lit. b.p. 100-102°C/1.5 mmHg [68JHC(5)785]}.

1- and 2-Trimethylsilyloxybutylbenzotriazole (**5.4a**) and(**5.4b**)

Prepared in quantitative yield, as a mixture of 1- and 2-isomers in the ratio (7 : 3) (as determined from the ^{1}H NMR spectrum), from (**5.1**) (0.52 g, 2.6 mmol) and butyraldehyde (0.19 g, 2.6 mmol). The two liquids were stirred together at room temperature under nitrogen for 42 hours; ν_{max} (neat) 1610w, 1585w, 1560w, 1100w, 1150w cm^{-1}; δ_H ($CDCl_3$) 8.3-7.3 (8 H, m, aromatic protons of benzotriazole ring in both isomers), 6.65-6.15 (2 H, m, 2 -C<u>H</u>-), 2.5-1.9 (4 H, m, 2 -C<u>H$_2$</u>-), 1.5-0.7 (10 H, m, other aliphatic protons), 0.1 (18 H, s, Si-C<u>H$_3$</u>); δ_C ($CDCl_3$) for 1-substituted isomer: 143.4 (C-3a), 130.6 (C-7a), 125.9 (C-6), 123.4 (C-5), 119.2 (C-4), 110.9 (C-7), 84.1 (-<u>C</u>H-O), 38.5, 17.3, 12.7; for 2-substituted isomer: 146.0 (C-3a), 126.6 (C-5), 117.8 (C-4), 88.3 (-<u>C</u>H-O), 38.7, 17.5, 12.7, -1.3 (Si-<u>C</u>H$_3$).

1-Trimethylsilyloxybenzylbenzotriazole (**5.5**)

Prepared according to the literature procedure [81JOM(208)309]. A mixture of equimolar amounts of (**5.1**) and freshly distilled benzaldehyde (3.1 mmol) was stirred for 24 hours (until solidification) under nitrogen at room temperature. The solid was hygroscopic and not stable enough to purify. Spectral characterization: δ_H ($CDCl_3$) 8.3-7.8 (1 H, m, H-4), 7.8-7.25 (9 H, m, other aromatic protons), 0.1 (9 H, s, Si-C<u>H$_3$</u>); δ_C ($CDCl_3$) 146.6 (C-3a), 137.8, 130.8 (C-7a), 128.6 (C-6), 128.2, 127.0, 125.4, 123.9 (C-5), 119.4 (C-4), 111.5 (C-7), 83.6 (-<u>C</u>H-O), -0.9 (Si-<u>C</u>H$_3$).

1-Benzylbenzotriazole (**5.6**)

Obtained as a major, unexpected product in the reaction of (**5.5**) with n-BuLi and benzyl bromide and in the reaction of (**5.1**) with cyclohexene-2-one and benzyl bromide. M.p. 116-117°C, lit. m.p. 115-116°C [56JCS1076]; (Found: C, 74.5; H, 5.4; N, 19.9. $C_{13}H_{11}N_3$ requires: C, 74.6; H, 5.3; N, 20.1%); δ_H ($CDCl_3$) 8.3-8.0 (1 H, m, H-4), 7.5-7.1

(8 H, m, other aromatic protons), 5.8 (2 H, s, -$\underline{CH}_2$-); δ_C ($CDCl_3$) 146.2 (C-3a), 132.6 , 131.2 (-7a), 128.8, 128.2 (C-6), 127.4, 123.7 (C-5), 119.8 (C-4), 109.6 (C-7), 52.0 (-$\underline{CH}_2$-).

3-(Benzotriazol-1-yl)-1-cyclohexanone (**5.8.1**)

1-Trimethylsilylbenzotriazole (**5.1**) (0.5 g, 2.6 mmol) was treated with an equimolar amount of freshly distilled cyclohexe-2-one added *via* syringe under nitrogen at room temperature. Heat was evolved. The mixture was stirred for 30 minutes and the resulting solid [silyl enol ether (**5.7.1**)] treated with 5 ml of HCl solution in water (1:9 by volume). The aqueous solution was extracted with $CHCl_3$ (3 x 10 ml), washed with water (20 ml), and dried ($MgSO_4$). Evaporation of the solvent yielded a viscous oil that was triturated with 30 ml of diethyl ether to give crystals (70%). M.p. 105-107°C (Found: C, 66.8; H, 6.2; N, 19.2. $C_{12}H_{13}N_3O$ requires: C, 67.0; H, 6.1; N, 19.5%); ν_{max} (neat) 1740s, 1610m, 1590m cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 8.07 (1 H, d, J = 8 Hz, H-4'), 7.61 (1 H, d, J = 8 Hz, H-7'), 7.55-7.30 (2 H, m, H-5',6'), 5.11 (1 H, septet, J = 4 Hz, H-3), 3.30 (1 H, dd, J = 14, and 10 Hz, -C$\underline{H}$-2, axial), 2.96 (1 H, dd, J = 14, 5 Hz, -C$\underline{H}$-2, equatorial), 2.58-3.34 (4 H, m), 2.23-1.81 (2 H, m); δ_C (50 MHz) ($CDCl_3$) 206.5 (C=O), 145.5 (C-3a), 131.8 (C-7a), 127.2 (C-6'), 123.9 (C-5'), 119.6 (C-4'), 109.0 (C-7'), 56.4 (-$\underline{C}$H-3), 46.3, 40.2, 30.5, 21.4.

3-(Benzotriazol-1-yl)-4,4-dimethylcyclohexanone (**5.8.2**)

To 1-trimethylsilylbenzotriazole (**5.1**) (0.37 g, 3.0 mmol) was added dropwise *via* a syringe under nitrogen an equimolar amount of 4,4-dimethylcyclohexen-2-one at room temperature. The temperature increased slightly upon addition. The mixture was stirred at room temperature for 6 hours (until it solidified). Then hydrochloric acid (5 ml, 1N) was added and the aqueous solution extracted with $CHCl_3$ (3 x 10 ml). The organic layer was washed with water (20 ml) and dried with $MgSO_4$. The oil obtained after solvent removal was purified by column chromatography using methylene chloride. Yield of the

pure ketone was 74%. M.p. 106-108°C (microcrystals from methanol) (Found: C, 68.8; H, 7.3; N, 17.0. $C_{14}H_{17}N_3O$ requires: C, 69.1; H, 7.0; N, 17.3%); ν_{max} (nujol) 1710s cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 8.06 (1 H, d, J = 8 Hz, H-4'), 7.61-7.34 (3 H, m, H-5'6'7'), 4.88 (1 H, dd, J = 9 Hz and 5 Hz, C<u>H</u>-3), 3.42 (1 H, dd, J = 16 Hz and 9 Hz, -C<u>H</u>-2 axial), 2.86 (1 H, dd, J = 9 Hz and 2 Hz, -C<u>H</u>-2 equatorial), 2.71-2.48 (2 H, m), 2.11-2.00 (1 H, m), 1.87-1.79 (1 H, m), 1.10 (6 H, d, J = 6 Hz, 2 C<u>H</u>$_3$); δ_C ($CDCl_3$) (50 MHz) 206.9 (C=O), 145.0 (C-3a), 133.7 (C-7a), 127.2 (C-6'), 123.8 (C-5'), 119.8 (C-4'), 109.5 (C-7'), 63.8 (-<u>C</u>H-3), 43.3, 37.2, 35.9, 35.5, 27.5, 21.9.

<u>3-(Benzotriazol-1-yl)-4-isopropylcyclohexanone (**5.8.3**)</u>

To 1-trimethylsilylbenzotriazole (**5.1**) (0.62 g, 3.26 mmol) was added *via* a syringe an equimolar amount of 4-isopropylcyclohexen-2-one under nitrogen at room temperature. The mixture was stirred for 48 hours. The thick oil was then treated with 10 ml of hydrochloric acid (1N) and extracted with $CHCl_3$ (3 x 10 ml). The organic layer was washed with water (20 ml) and dried ($MgSO_4$). After solvent removal the residue was purified by column chromatography, using $CHCl_3$ - ethyl acetate (9:1) as eluent. The *trans* isomer (**5.8.3a**) was eluted first (R_f = 0.4), followed by the *cis* isomer (**5.8.3b**) (R_f = 0.23).

<u>3-*trans*-(Benzotriazol-1-yl)-4-isopropylcyclohexanone (**5.8.3a**)</u>

Obtained in 22% yield from column chromatography, as microcrystals m.p. 104-106°C (methanol) (Found: C, 70.1; H, 7.7; N, 16.2. $C_{15}H_{19}N_3O$ requires: C, 70.1; H, 7.4; N, 16.3%); ν_{max} (nujol) 1720s, 1620m, 1590m cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 8.10 (1 H, d, J = 8 Hz, H-4'), 7.61-7.33 (3 H, m, H-5'6'7'), 4.98 (1 H, sextet, J = 5 Hz, -C<u>H</u>-3), 3.40-3.27 (1 H, m), 2.92-2.59 (4 H, m), 2.22-2.13 (1 H, m), 1.74-1.52 (1 H, m), 1.27-1.20 (1 H, m), 0.92 (3 H, d, J = 7 Hz, -CH$_3$), 0.76 (3 H, d, J = 7 Hz, -CH$_3$); δ_C ($CDCl_3$) 206.7

(C=O), 145.6 (C-3a), 132.4 (C-7a), 127.5 (C-6'), 124.0 (C-5'), 120.1 (C-4'), 108.7 (C-7'), 58.6 (-CH-3), 47.3, 46.2, 40.3, 26.1, 21.7, 20.8, 15.7.

3-*cis*-(Benzotriazol-1-yl)-4-isopropylcyclohexanone (**5.8.3b**)

Obtained in (7%) yield from column chromatography, as plates (methanol) (Found: C, 70.0; H, 7.7; N, 16.2. $C_{15}H_{19}N_3O$ requires: C, 70.1; H, 7.4; N, 16.3%); ν_{max} (nujol) 1710s, 1615w, 1590w cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 8.07 (1H, m, H-4'), 7.52-7.29 (3 H, H-5'6'7'), 5.48 (1 H, m, -CH-3), 2.94-2.08 (7 H, m), 1.26-1.19 (1 H, m), 0.99-0.96 (3 H, m, $-CH_3$), 0.68-0.65 (3 H, m, $-CH_3$); δ_C (50 MHz) ($CDCl_3$) 206.5 (C=O), 145.0 (C-3a), 133.6 (C-7a), 127.4 (C-6'), 123.9 (C-5'), 120.1 (C-4'), 108.9 (C-7'), 57.4 (-CH-3), 46.6, 46.4, 40.2, 28.8, 24.1, 21.8, 19.8.

3-[(Benzotriazol-1-yl)phenylmethyl]pentan-2,4-dione (**5.8.4**)

To 1-trimethylsilylbenzotriazole (**5.1**) (0.63 g, 3.3 mmol) was added *via* a syringe 3-benzylidenepentane-2,4-dione (0.58 g, 3.3 mmol) under nitrogen and at room temperature. The mixture was stirred for 24 hours and a catalytic amount of zinc chloride (100 mg) in 4 ml of chloroform was added. The suspension was stirred for an additional 70 hrs. After that time the mixture was treated with saturated solution of NH_4Cl (10 ml) and extracted with $CHCl_3$ (3 x 10 ml). The organic layer was washed with water (20 ml) and dried ($MgSO_4$). After solvent removal, the crude residue was purified by column chromatography on silica gel (60-200 mesh) with benzene as an eluent. The product was obtained (22%) as a solid, m.p. 128-130°C (needles) (Found: C, 70.4; H, 5.8; N, 13.5. $C_{18}H_{17}N_3O_2$ requires: C, 70.3; H, 5.6; N, 13.7%); ν_{max} (nujol) 1735s, 1705s, 1620w, 1590w cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 8.02 (1 H, d, J = 8 Hz, H-4'), 7.47-7.26 (8 H, m, other aromatic protons), 6.45 (1 H, d, J = 11 Hz, -CH-Ph), 5.70 (1 H, d, J = 11 Hz -CH-CH-), 2.33 (3 H, s, $-CH_3$), 2.10 (3 H, s, $-CH_3$); δ_C (50 MHz) ($CDCl_3$) 199.4 (C=O),

198.7 (C=O), 145.8 (C-3a), 135.6, 132.5 (C-7a), 128.9, 128.85, 127.5 (C-6'), 124.1 (C-5'), 119.5 (C-4'), 109.6 (C-7'), 71.5 (-CH-Ph), 61.3 (-CH-CH), 31.5 (-CH_3), 30.4 (-CH_3).

N-Benzoylbenzotriazole (**5.9**)

A solution of silyl enol ether (**5.7.1**), prepared from equimolar amounts (4.6 mmol) of (**5.1**) and cyclohehexen-2-one, in 4.5 ml of methylene chloride was added dropwise under argon to the freshly distilled benzoyl chloride (4.6 mmol) in 4.5 ml of CH_2Cl_2. The mixture was stirred at room temperature for 24 hours. The solvent was then removed and the residue was recrystallized from methanol (74%). M.p. 111-112°C (needles) (Found: C, 69.5; H, 4.0; N, 18.7. $C_{13}H_9N_3O$ requires: C, 69.9; H, 4.1; N, 18.8%); ν_{max} (KBr) 1705m, 1595w cm^{-1}; δ_H ($CDCl_3$) 8.6-8.1 (5 H, m), 7.9-7.3 (4 H, m); δ_C ($CDCl_3$) 166.4 (C=O), 145.5 (C-3a), 133.4, 131.9 (C-7a), 131.6, 131.3, 130.1, 128.2 (C-6), 126.1 (C-5), 119.9 (C-4), 114.6 (C-7).

3-[(Benzotriazol-1-yl)-2-(4-methylphenylmethylidene)]cyclohexanone (**5.11**)

A solution of the silyl enol ether (**5.7.1**) (5.4 mmol in 3 ml of CH_2Cl_2) prepared from equimolar amounts of (**5.1**) and cyclohexen-2-one was cooled to -60°C and added dropwise to a mixture of p-methylbenzaldehyde (0.64 g, 5.4 mmol) and $TiCl_4$ (5.4 ml, 5.4 mmol) at the same temperature. The mixture was warmed up to room temperature. After 1 hr it was poured into 30 ml of water and extracted with methylene chloride (3 x 15 ml). The organic layer was washed with water (30 ml) and dried with $MgSO_4$, concentrated under vacuum and purified by column chromatography. Rechromatography was necessary to separate (**5.8.1**). The viscous oil crystallized out as plates (20%), m.p. 133-135°C (methanol) (Found: C, 75.9; H, 6.0; N, 13.0. $C_{20}H_{19}N_3O$ requires: C, 75.7; H, 6.0; N, 13.2%); ν_{max} (neat) 1675s, 1605s, 1510s, cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 8.05 (1 H, d, J = 8 Hz, H-4), 7.43-7.05 (8 H, m), 6.80 (1 H, m), 2.57-2.38 (4 H, m), 2.3 (3 H, s,

-C<u>H</u>$_3$), 2.29-1.91 (2 H, m); δ_C ($CDCl_3$) 196.9 (C=O), 150.5 (<u>C</u>H=C), 145.8 (-3a), 138.0, 137.4, 133.7 (<u>C</u>=CH), 132.6 (C-7a), 129.4, 127.5, 127.1 (C-6'), 123.7 (C-5'), 119.6 (C-4'), 109.9 (C-7'), 59.0 (<u>C</u>H-3), 37.9, 25.9, 22.3, 20.9.

CHAPTER VI
N-MONOMETHYLATION OF PRIMARY AMINES *VIA* INTERMEDIATE BENZOTHIAZOL-2(3H)-IMINES

6.1 Introduction

6.1.1 Reactivity of 2-Mercaptobenzothiazole Derivatives Towards Nucleophiles

It has been shown previously that S-alkyl derivatives of 2-mercaptobenzothiazole are easily replaced by variety of nucleophilic reagents (Figure 6.1). The synthesis of

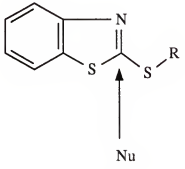


Figure 6.1

alkyl or aryl substituted heterocycles was easily achieved using nickel catalyzed coupling between 2-thiomethylbenzothiazole and a variety of Grignard reagents [79CL1447]. Efficient control of regioselectivity in the allylic cross-coupling with Grignard reagents in the presence of CuBr has been accomplished using 2-allylthiobenzothiazoles as

electrophiles [83JCS(P1)2953]. In recent work Katritzky *et al.* developed a novel method for mercaptomethylation of alkyl halides, aromatic aldehydes and ketones using lithio derivatives of 2-methylthiobenzothiazole (Figure 6.2) [87JCS(P1)769].

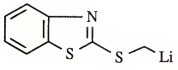


Figure 6.2

The ability of alkyllithiums to convert 2-(alkylthio)- and 2-(alkynylthio)-benzothiazoles into alkyl and alkenyl mercaptans was further developed by utilizing the reactivity of the trimethylsilyl group in 2-[(α-silylalkyl)thio]benzothiazoles (Figure 6.3)

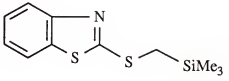


Figure 6.3

[87JOC(52)844]. This sequence provides a general method for mercaptoalkylation of carbonyl compounds. In both cases, the 2-alkylthiobenzothiazole acted as a protected thiol. Likewise, 2-substituted-3-methyl-2,3-dihydrobenzothiazoles have been used as protected forms of the carbonyl functionality. Corey and Boger, in a series of papers [78TL5, 9, 13], described a method for introducing two-carbon units into carbonyl

compounds using the benzothiazole moiety. Chicashita and coworkers utilized 3-methyl-benzothiazolines as a convenient type of protection for carbonyl groups [85H(23)295, 85H(23)2509, 86H(24)279]. This method allowed for efficient protection and deprotection under mild, neutral conditions and also provided selective protection of aldehydic groups in the presence of a ketone functionality.

6.1.2 General Methods for N-Monoalkylation of Primary Amines

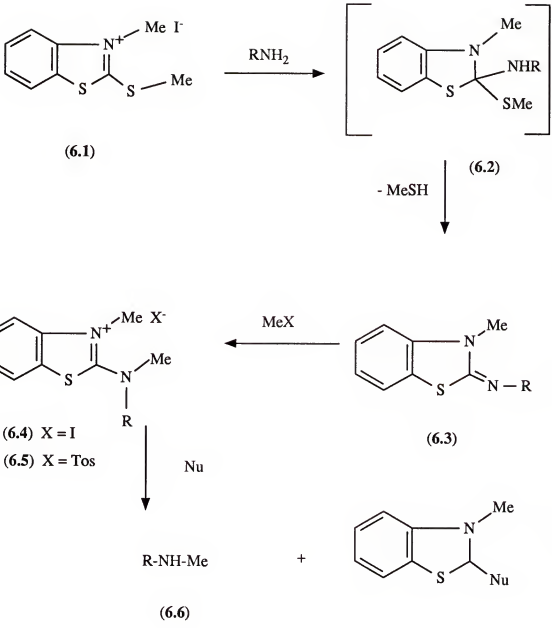
N-Monoalkylation of primary amines is one of the most important functional group transformations in organic synthesis. There are many methods available in the literature for N-monoalkylation of primary amines. Most methods that utilize electrophilic alkylating agents [recent papers include: 82CJC(60)1815, 82CL1783, 83SC601, 85TL297] suffer from serious limitations. These limitations include competing bisalkylation, poor yields, drastic reaction conditions (high temperatures, sealed tubes, *etc*). In particular, none of the published procedures offer simultaneous mild reaction conditions and simple, readily available reagents.

There are several conceptually different approaches to the problem available. One of them is reduction of imine derivatives of primary amines [40JA(62)922, 74S55]. Another, more effective way is reduction of N-acyl derivatives of primary amines. In 1982 Krishnamurthy reported the selective reaction of primary aliphatic and aromatic amines with an excess of acetic formic anhydride to yield the corresponding formamide intermediates. These intermediates were subsequently reduced to the N-methylamines with a borane-methyl sulfide complex [82TL3315]. Analogously, refluxing primary or secondary amines with a carboxylic acid and trimethylamine borane in xylene led to the corresponding N-alkylated amines [83S1013]. Only moderate yields were obtained for primary amines and bis alkylation products were isolated.

Diisobutylaluminum hydride was used as a selective reagent for reduction of oximes to secondary amines [83TL4711]. Another, more recent approach, involves nucleophilic addition of organometallic reagents such as organolithium or organomagnesium reagents to formaldehyde imine intermediates. Indeed, monoalkylation of aliphatic and aromatic primary amines was accomplished by the reaction of organolithium or Grignard reagents with N-(cyanomethyl) or N-(methoxymethyl) derivatives [83CC1109, 84TL1635]. However, use of cyanide as a leaving group was potentially complicated by the competing addition of the organometallic reagent to the nitrile group. N-Monoalkylation of aromatic and heteroaromatic amines was successfully achieved in high yields when adducts formed from benzotriazole, aliphatic aldehydes and amines were treated with sodium borohydride or Grignard reagents [87JCS(P1)805].

6.1.3 Aim of the Work

We wanted to develop a method for N-monomethylation of primary amines using conventional electrophilic alkylating agents under mild conditions and utilizing the benzothiazole moiety as a protecting group for the NH_2 functionality. We have found that primary aliphatic and aromatic amines react with 3-methyl-2-methylthiobenzothiazolium iodide to form imines (**6.3**) in high yields with expulsion of methyl mercaptan. Such compounds could be easily methylated on the imino nitrogen by methyl iodide or methyl p-toluenesulfonate to afford the corresponding 3-methyl-2-(substituted amino)-benzothiazolium salts. Nucleophilic attack on the 2-position of the benzothiazole ring would be facilitated by the positively charged nitrogen. Therefore, cleavage of the heterocyclic protecting group would liberate the N-monomethylated amine (**6.6**) (Scheme 6.1).


Me I-
N+
S
S
Me
RNH2
Me
N
NHR
S
SMe
(6.1)
(6.2)
- MeSH
Me X-
N+
Me
S
N
R
MeX
Me
N
S
N — R
(6.4) X = I
(6.5) X = Tos
(6.3)
Nu
R-NH-Me
+
Me
N
S
Nu
(6.6)

Scheme 6.1

6.2 Results and Discussion

6.2.1 Formation of 3-Methylbenzothiazol-2(3*H*)-Imines (**6.3**)

3-Methylbenzothiazol-2(3*H*)-imines (**6.3**) formed readily at room temperature in dichloromethane upon addition to (**6.1**) of two moles of a primary aliphatic amine or of one mole each of an aromatic amine and triethylamine. The use of triethylamine instead of a second mole of aromatic amine is required to complete the reaction since the aromatic amine is not basic enough to promote β-elimination from intermediate (**6.2**). The imines (**6.3**) were obtained in very good yields (Table 6.1).

Table 6.1 Preparation of the 3-Methylbenzothiazol-2(3*H*)-Imines (**6.3**)

Compound	Amine	Method	Yield (%)	B.p.(°C/mmHg) or m.p.(°C)
(6.3.1)	Octylamine	A[a]	95	130-137/0.5
(6.3.2)	Dodecylamine	A	95	140-150/2.0
(6.3.3)	Cyclohexylamine	A	92	115-120/2.0
(6.3.4)	Phenethylamine	A	98	150-160/2.5-3.0
(6.3.5)	Aniline	B[b]	98	96-98 (EtOH)
(6.3.6)	p-Toluidine	B	98	89-91 (EtOH)

[a]Method A used 2 equivalents of the parent amine [b]Method B used 1 equivalent of triethylamine (see Experimental).

All synthesized imines (**6.3**) were characterized by their spectral (IR, ^{1}H, and ^{13}C NMR) properties as well as elemental analyses (C, H, N). All of the imines showed a strong absorption in the region 1635-1610 cm^{-1} of their IR spectra due to the C=N stretching vibrations. The ^{13}C NMR spectra of the compounds (**6.3**) displayed characteristic pattern for the benzothiazole quaternary carbons and for C-4 (see Figure 6.4 for the numbering in the benzothiazole nucleus). Thus, C-2, C-3a, and C-7a appeared at δ 157.0-153.4, 141.3-140.5, and 122.5-122.2 ppm, respectively, whereas C-4 was significantly shielded [79OMR(12)499] at δ 108.9-108.0 ppm (Table 6.2). Chemical

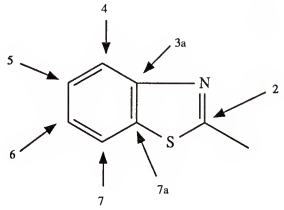


Figure 6.4

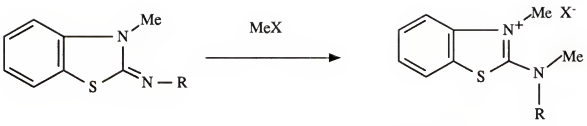
shifts of the aliphatic carbons attached to the imine nitrogen in compounds (**6.3.1**)-(**6.3.4**) appeared in the region δ 64.4 ppm (CH) and δ 54.9 ppm (CH_2). The methyl groups attached to the ring nitrogen were found in the region δ 37.3-30.3 ppm. The ^{1}H NMR spectra of the imines (**6.3**) showed aromatic absorption between δ 7.5 ppm and δ 6.7 ppm, with H-4 of the benzothiazole ring appearing furthest upfield at about δ 6.8 ppm.

Table 6.2. Chemical Shifts of Benzothiazole Carbons in Imines (**6.3**)

Compound	C-2	C-3a	C-4	C-5	C-6	C-7	C-7a
(6.3.1)	155.5	141.1	108.3	126.1	121.9	120.5	122.5
(6.3.2)	155.4	141.3	108.2	126.0	121.9	120.4	122.5
(6.3.3)	153.4	141.2	108.0	125.9	121.8	120.3	122.5
(6.3.4)	155.7	140.9	108.1	125.8	121.8	120.3	122.2
(6.3.5)	157.0	140.5	108.8	126.1	123.5	121.5	122.2
(6.3.6)	157.0	140.7	108.9	126.2	122.1	121.6	122.4

6.2.2 Methylation of the Imine Nitrogen in Compounds (**6.3**)

Methylation of benzothiazol-2(3*H*)-imines derived from aliphatic amines proceeded smoothly in refluxing methyl iodide over a period of 45 hours to give iodides (**6.4**). Under these conditions, methylation of imines derived from aromatic amines were too slow to be of preparative utility. However, these conversions were conveniently carried out by heating the imine and methyl p-toluenesulfonate together at 100°C for 1 hour to form salts (**6.5**). This second method is general since it also worked satisfactorily with aliphatic amines (Scheme 6.2) (Table 6.3).



(**6.3**)

(**6.4**) X = I

(**6.5**) X = Tos

Scheme 6.2

Table 6.3 Preparation of Imminium Salts (**6.4**) and (**6.5**)

Imminium Salt	Starting Imine	Yield (%)	Anion	M.p. (°C)
(**6.4.1**)	(**6.3.1**)	94	I^-	107-114
(**6.4.2**)	(**6.3.2**)	92	I^-	123-125
(**6.4.3**)	(**6.3.3**)	99	I^-	176-178
(**6.5.1**)	(**6.3.4**)	94	Tos^-	145-147
(**6.5.2**)	(**6.3.5**)	96	Tos^-	152-154
(**6.5.3**)	(**6.3.6**)	95	Tos^-	186-188

Compounds (**6.4**) and (**6.5**) were fully characterized by their spectral and analytical data. A large downfield shift in the ^{13}C NMR spectra of the imminium salts (**6.4**) and (**6.5**) was observed for the benzothiazole C-2 (δ 170 ppm) with respect to the same carbon

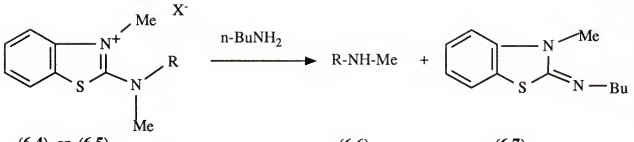
in the corresponding imines. Peaks for C-3a and C-7a remained at about the same chemical shifts. The C-4 signal was also shifted downfield to δ 114.1-113.8 ppm (Table 6.4). There was no significant change in the chemical shift of the aliphatic carbon attached to the outer nitrogen. The methyl group bonded to the ring nitrogen was deshielded to the region δ 47.4-39.9 ppm since this nitrogen became positively charged.

Table 6.4 Chemical Shifts of Benzothiazole Carbons in the Compounds (**6.4**) and (**6.5**)

Compound	C-2	C-3a	C-4	C-5	C-6	C-7	C-7a
(6.4.1)	170.6	140.4	114.1	128.4	125.8	122.6	121.4
(6.4.2)	170.6	140.4	114.1	128.4	125.8	122.5	121.5
(6.4.3)	170.7	140.2	114.1	128.2	125.6	122.4	121.4
(6.5.1)	170.6	140.2	113.8	126.7	125.4	121.9	121.7
(6.5.2)	169.6	140.3	114.0	128.3	125.8	122.5	122.7
(6.5.3)	170.0	140.6	114.1	128.5	125.9	122.5	122.6

6.2.3 Preparation of N-Monomethylated Amines (**6.6**)

Liberation of the N-methylated amines (**6.6**) from amidinium salts (**6.4**) and (**6.5**) was achieved by treatment with one equivalent of n-butylamine in dichloromethane at 25°C (Scheme 6.3). The side product, 2-butylimino-3-methylbenzothiazole (**6.7**) was easily separated from the major product.



(**6.4**) or (**6.5**) (**6.6**) (**6.7**)

Scheme 6.3

Table 6.5 Preparation of N-Monomethylated Amines R-NH-Me (**6.6**)

Amine	R	Yield (%)	B.p. (°C/mmHg)	Lit. B.p. (°C/mmHg)	Reference
(**6.6.1**)	C_8H_{17}-	88	125-135/90	77.5-80/17	52JA(74)1704
(**6.6.2**)	$C_{12}H_{25}$-	85	110-120/1.5	175-176/760	55MI153
(**6.6.3**)	C_6H_{12}-	83	110-120/200	61-63/35	82MI3810
(**6.6.4**)	$Ph(CH_2)_2$	85	110-115/35-40	112-115/36-40	82MI4624
(**6.6.5**)	Ph	88	80-90/15	79.2/10	82MI3731
(**6.6.6**)	p-Me-Ph	84	92-95/8	98-99/19	82MI2068

All N-monomethylated amines were characterized by their spectral properties and by comparison of their boiling points with previously reported literature data (Table 6.5). The N-monoalkylated amine products were separated from (**6.7**) by three different

methods. Compounds (**6.6.1**), (**6.6.3**), and (**6.6.4**) were purified by direct distillation from the reaction mixture (see Experimental for details). Amines (**6.6.5**) and (**6.6.6**) were separated from (**6.7**) by column chromatography on silica gel using methylene chloride as eluent. Product (**6.6.2**) was precipitated from the reaction mixture as a hydroiodide. N-Methyldodecylamine (**6.6.2**) was then regenerated by basification with potassium hydroxide.

6.3 Conclusions

The use of N-methylbenzothiazol-2(3*H*)-imines derived from primary aliphatic and aromatic amines allowed exclusive monomethylation at the imino nitrogen. These N-methylated amines were easily liberated from this masked form and isolated in high overall yields. This three-step sequence is general for both aliphatic and aromatic amines, and, with exception of the methylation of amidines derived from aromatic amines, all the steps could be performed at or near room temperature. The reagents used in this procedure are common and easily accessible. This new method allows monomethylation of primary amines in good yields under mild reaction conditions.

6.4 Experimental

Apparatus and general procedures used in this Chapter are identical to those described in Chapter V with addition that elemental analyses of the liquid samples were carried in Atlantic Microlab, Inc. in Atlanta, Georgia.

3-Methyl-2-methylthiobenzothiazolium iodide (**6.1**) was prepared according to the literature procedure [51JCS1716]. M.p. 145-147°C, literature m.p. 148°C.

6.4.1 General Procedure for the Preparation of N-Methylbenzothiazoline-2-imines (**6.3**)

Method A

The aliphatic primary amine (18 mmol) was added to a stirred suspension of 3-methyl-2-methylthiobenzothiazolium iodide (**6.1**) (2.9 g, 9 mmol) in methylene chloride (45 ml) and the mixture was stirred at 25°C for the appropriate time (see below). The reaction mixture was then extracted with water (3 x 50 ml), the organic layer dried ($MgSO_4$) and the solvent evaporated to afford the amidines (**6.3**), that were pure (TLC and ^1H NMR) in most cases.

Method B

The aromatic primary amine (9 mmol) and triethylamine (9 mmol) were added to a stirred suspension of 3-methyl-2-methylthiobenzothiazolium iodide (**6.1**) (2.9 g, 9 mmol) in methylene chloride (45 ml) and the mixture was stirred at 25°C for the appropriate time (see below). The reaction mixture was then extracted with water (3 x 50 ml), the organic layer dried ($MgSO_4$) and the solvent evaporated to afford the amidines (**6.3**).

3-Methyl-3*H*-benzothiazoline-2-[N-(1-octyl)]imine (**6.3.1**)

Prepared (95%) from n-octylamine after 3 hours of stirring, as an oil, b.p. (Kugelrohr) 130-137°C/0.5 mmHg (Found: C, 69.5; H, 8.7; N, 10.1. $C_{16}H_{24}N_2S$ requires: C, 69.6; H, 8.7; N, 10.1%); ν_{max} (neat) 1630s, 1585s cm^{-1}; δ_H ($CDCl_3$) 7.6-6.9 (4 H, m, benzothiazole ring protons), 3.5 (3 H, s, N-C<u>H</u>$_3$), 3.3 (2 H, t, J = 7 Hz, =N-C<u>H</u>$_2$-CH_2), 1.9-0.8 (15 H, m, aliphatic chain protons); δ_C (50 MHz) ($CDCl_3$) 155.5 (C-2), 141.1 (C-3a), 126.1 (C-5), 122.5 (C-7a), 121.9 (C-6), 120.5 (C-7), 108.3 (C-4), 54.9 (N-<u>C</u>H$_2$-), 31.7 (N-<u>C</u>H$_3$), 30.8, 29.7, 29.6, 29.3, 29.1, 22.5, 13.9 (unassigned chemical shifts of the carbons of the aliphatic chain).

3-Methyl-3*H*-benzothiazoline-2-[N-(1-dodecyl)]imine (**6.3.2**)

Prepared (95%) from n-dodecylamine after 4 hours of stirring, as an oil, b.p. (Kugelrohr) 140-150°C/2 mmHg; (Found: M^+, 332.2274, calculated for $C_{20}H_{32}N_2S$: M^+, 332.2286); ν_{max} ($CHBr_3$) 1630s, 1585s cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 7.31-6.79 (4 H, m, benzothiazole ring protons), 3.43 (3 H, s, N-C$\underline{H}_3$), 3.19 (2 H, t, J = 7 Hz, =N-C$\underline{H}_2$-CH_2), 1.72-1.65 (2 H, m, =N-CH_2-C$\underline{H}_2$-), 1.44-1.27 (18 H, m, protons of the methylene groups), 0.92-0.86 (3 H, m, methyl group); δ_C (50 MHz) ($CDCl_3$) 155.4 (C-2), 141.3 (C-3a), 126.0 (C-5), 122.5 (C-7a), 121.9 (C-6), 120.4 (C-7), 108.2 (C-4), 55.15 (N-$\underline{C}H_2$), 31.9 (N-$\underline{C}H_3$), 29.8, 29.6, 29.5, 29.3, 27.5, 22.7, 14.1.

3-Methyl-3*H*-benzothiazoline-2-(N-cyclohexyl)imine (**6.3.3**)

Prepared from cyclohexylamine after 8 hours. The oil was purified by column chromatography (chloroform as eluent) to afford pure product (98%), b.p. (Kugelrohr) 115-120°C/2 mmHg (Found: C, 68.2; H, 7.3; N, 11.3. $C_{14}H_{18}N_2S$ requires: C, 68.2; H, 7.3; N, 11.4%); ν_{max} (neat) 1610s, 1580s cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 7.27-6.75 (4 H, m, protons of the benzothiazole ring), 3.35 (3 H, s, N-C$\underline{H}_3$), 2.98-2.78 (1 H, m, C$\underline{H}$), 1.81 (5 H, m) and 1.39-1.37 (5 H, m, protons of the cyclohexyl ring); δ_C (50 MHz) ($CDCl_3$) 153.4 (C-2), 141.2 (C-3a), 125.9 (C-5), 122.5 (C-7a), 121.8 (C-6), 120.3 (C-7), 108.0 (C-4), 64.4 (N-$\underline{C}$H), 33.8 (N-$\underline{C}H_3$), 30.1, 25.7, 25.0 (unassigned chemical shifts of the carbons in the cyclohexyl ring).

3-Methyl-3*H*-benzothiazoline-2-[N-(2-phenethyl)]imine (**6.3.4**)

Prepared (98%) from 2-phenethylamine after 3 hours, as a yellowish oil, b.p. (Kugelrohr) 150-160°C/2.5-3 mmHg (Found: C, 71.4; H, 6.1; N, 10.4). $C_{16}H_{16}N_2S$ requires: C, 71.6; H, 6.0; N, 10.4%); ν_{max} (neat) 1625s, 1580s cm^{-1}; δ_H ($CDCl_3$) 7.2-6.25 (9 H, m, all aromatic protons), 3.5-2.5 (7 H, m, all aliphatic protons); δ_C (50 MHz)

($CDCl_3$) 155.7 (C-2), 140.9, 128.7, 128.2, 125.9, 125.8, 122.2, 121.8, 120.3, 108.1, (other aromatic carbons), 56.4 (N-$\underline{C}H_2$), 37.3 (N-$\underline{C}H_3$), 29.8 (N-CH_2-$\underline{C}H_2$-).

3-Methyl-3*H*-benzothiazoline-(N-phenyl)imine (**6.3.5**)

Prepared (98%) from aniline after 8 hours, as white microcrystals, m.p. 96-98°C (from ethanol) (Found: C, 70.0; H, 5.1; N, 11.5. $C_{14}H_{12}N_2S$ requires: C, 70.0; H, 5.0; N, 11.6%); ν_{max} ($CHBr_3$) 1620s, 1580s cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 7.38-6.87 (9 H, m, all aromatic protons), 3.53 (3 H, s, N-$\underline{C}H_3$); δ_C (50 MHz) ($CDCl_3$) 157.0 (C-2), 151.1, 140.5, 129.4, 126.1, 123.5, 122.2, 121.9, 121.5, 121.4, 108.8, 30.3 (N-$\underline{C}H_3$).

3-Methyl-3*H*-benzothiazoline-2-[N-(4-methylphenyl)]imine (**6.3.6**)

Prepared from p-toluidine after 8 hours. The residue after evaporation of the solvent was triturated in ethanol to afford pure product (94%), m.p. 89-91°C (Found: C, 70.6; H, 5.5; N, 11.0. $C_{15}H_{14}N_2S$ requires: C, 70.8; H, 5.55; N, 11.0%); ν_{max} ($CHBr_3$) cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 7.23-6.84 (8H, m, all aromatic protons), 3.50 (3 H, s, N-$\underline{C}H_3$), 2.32 (3 H, s, $\underline{C}H_3$); δ_C (50 MHz) ($CDCl_3$) 157.0 (C-2), 148.8, 140.7, 133.0, 130.2, 126.2, 122.4, 122.1, 121.6, 121.3, 108.9, (other aromatic carbons), 30.5 (N-$\underline{C}H_3$), 21.1 (CH_3).

6.4.2 General Procedure for the Methylation of Imines (**6.3**)

Iodine salts (**6.4**)

The imine (**6.3**) (4.18 mmol), was refluxed in methyl iodide (20 ml) for 45 hours. The solvent was distilled off and the solid remaining triturated with diethyl ether, filtered and washed with ether to afford the pure (based on TLC and ^1H NMR) iodides (**6.4**).

p-Methylbenzenesulfonate salts (**6.5**)

The imine (**6.3**) (1 mmol) was mixed with methyl p-methylbenzenesulfonate (1.6 mmol) and the mixture heated at 100°C for 1 h. The gummy material that resulted was

triturated with diethyl ether and the white solid obtained was then filtered off and washed thoroughly with ether. This gave the pure (based on TLC and ^1H NMR) salts (**6.5**).

3-Methyl-2-[N-methyl-N-(1-octylamino]benzothiazolium iodide (**6.4.1.**)

Prepared (94%) from (**6.3.1**), m.p. 107-114°C (Found: C, 48.8; H, 6.6; N, 6.6. $C_{17}H_{27}IN_2S$ requires: C, 48.8; H, 6.45; N, 6.7%); ν_{max} ($CHBr_3$) 1605m, 1570m cm^{-1}; δ_H ($CDCl_3$) 8.3-7.5 (4 H, m, protons of the benzothiazole ring), 4.3 (3 H, s, N^+-C<u>H</u>$_3$), 3.9 (2 H, t, J = 6 Hz, N-C<u>H</u>$_2$-), 3.75 (3 H, s, N-C<u>H</u>$_3$), 1.9-1.8 (2 H, m, N-CH_2-C<u>H</u>$_2$), 1.7-0.8 (13 H, m, unassigned aliphatic protons); δ_C (50 MHz) ($CDCl_3$) 170.6 (C-2), 140.4 (C-3a), 128.4 (C-5), 125.8 (C-6), 122.6 (C-7), 121.4 (C-7a), 114.1 (C-4), 58.8 (N-C<u>H</u>$_2$-), 43.3 (N^+-C<u>H</u>$_3$), 39.3 (N-C<u>H</u>$_3$), 31.2, 28.65, 28.6, 26.3, 26.1, 22.1, 13.6 (unassigned chemical shifts of the aliphatic carbons).

3-Methyl-2-[N-methyl-N-(1-dodecylamino]benzothiazolium iodide (**6.4.2**)

Prepared (92%) from (**6.3.2**), m.p. 123-125°C (Found: C, 53.0; H, 7.6; N, 5.8. $C_{21}H_{35}IN_2S$ requires: C, 52.9; H, 7.8; N, 5.9%); ν_{max} ($CHBr_3$) 1605s, 1580s cm^{-1}; δ_H ($CDCl_3$) 8.2-7.3 (4 H, m, protons of the benzothiazole ring), 4.3 (3 H, s, N^+-C<u>H</u>$_3$), 4.0-3.6 (5 H, m, N-C<u>H</u>$_3$ and N-C<u>H</u>$_2$-), 2.0-1.1 (20 H, m, unassigned methylene protons of the aliphatic chain), 0.9-0.8 (3 H, m, -C<u>H</u>$_3$); δ_C (50 MHz) ($CDCl_3$) 170.6 (C-2), 140.4 (C-3a), 128.4 (C-5), 125.8 (C-6), 122.5 (C-7), 121.5 (C-7a), 114.1 (C-4), 58.9 (N-C<u>H</u>$_2$-), 43.3 (N^+-C<u>H</u>$_3$), 39.4 (N-C<u>H</u>$_3$), 31.4, 29.0, 28.9, 28.7, 26.3, 26.1, 22.2, 13.7 (unassigned chemical shifts of the aliphatic carbons).

3-Methyl-2-(N-methyl-N-cyclohexylamino)benzothiazolium iodide (**6.4.3**)

Prepared (99%) from (**6.3.3**), m.p. 176-178°C (Found: C, 46.15; H, 5.5; N, 7.0. $C_{15}H_{21}IN_2S$ requires: C, 46.4; H, 5.45; N, 7.2%); ν_{max} ($CHBr_3$) 1590m, 1560s cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 7.92 (1H, d, J = 8 Hz, H-7), 7.65-7.50 (2 H, m, H-5,6), 7.43 (1 H, d, J = 8 Hz, H-4), 4.18 (3 H, s, N^+-C<u>H</u>$_3$), 3.90-3.80 (1 H, m, N-C<u>H</u>-), 3.51 (3 H, s, N-C<u>H</u>$_3$),

2.30-1.50 (10 H, m, unassigned cyclohexyl protons); δ_C (50 MHz) ($CDCl_3$) 170.7 (C-2), 140.2 (C-3a), 128.2 (C-5), 125.6 (C-6), 122.4 (C-7), 121.4 (C-7a), 114.1 (C-4), 66.7 (N-CH-), 39.9 (N^+-CH_3), 37.5 (N-CH_3), 29.0 , 24.6, 24.3 (unassigned chemical shifts of the carbons in cyclohexyl substituent).

3-Methyl-2-[N-methyl-(2-phenylethyl)amino]benzothiazolium p-methylbenzenesulfonate **(6.5.1)**

Prepared (94%) from **(6.3.4)** m.p. 145-147°C (Found: C, 63.0; H, 6.0; N, 6.1. $C_{24}H_{26}N_2O_3S_2$ requires: C, 63.4; H, 5.8; N, 6.2%); ν_{max} ($CHBr_3$) 1580 cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 7.66-6.93 (13 H, m, all aromatic protons), 3.90-3.70 (5 H, m, N^+-CH_3 and N-CH_2-), 3.45 (3 H, s, N-CH_3), 2.99 (2 H, m, -CH_2-), 2.20 (3 H, s, -CH_3); δ_C (25 MHz) ($CDCl_3$) 170.6 (C-2), 143.5, 140.2, 138.6, 136.4, 128.4, 128.0 , 126.7, 125.4, 121.9, 121.7, 113.8, (other aromatic carbons), 59.3 (N-CH_2-), 42.5 (N^+-CH_3), 37.5 (N-CH_3), 32.4 (CH_2-CH_2), 20.8 (-CH_3).

3-Methyl-2-[(N-methyl-N-phenylamino)]benzothiazolium p-methylbenzenesulfonate **(6.5.2)**

Prepared (96%) from **(6.3.5)**, m.p. 152-154°C (Found: C, 62.3; H, 5.3; N, 6.6. $C_{22}H_{22}N_2O_3S_2$ requires: C, 61.9; H, 5.2; N, 6.6%); ν_{max} ($CHBr_3$) 1595m, 1565m cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 7.74 (2 H, d, J = 8 Hz), 7.58-7.36 (9 H, m, aromatic protons), 6.88 (2 H, d, J = 8 Hz), 3.78 (3 H, s, N^+-CH_3), 3.42 (3 H, s, N-CH_3), 2.19 (3H, s, -CH_3); δ_C (50 MHz), ($CDCl_3$) 169.6 (C-2), 144.2, 143.2, 140.3, 138.1, 130.4, 129.2, 128.3, 127.9, 125.8, 125.6, 125.5, 122.7, 122.5, 114.0, (other aromatic carbons), 47.2 (N^+-CH_3), 40.0 (N-CH_3), 20.9 (-CH_3).

3-Methyl-2-[N-methyl-N-(4-methylphenyl)amino]benzothiazolium p-methylbenzene-sulfonate **(6.5.3)**

Prepared (95%) from **(6.3.6)**, m.p. 186-188°C (Found: C, 63.1; H, 5.7; N, 6.2. $C_{23}H_{24}N_2O_3S_2$ requires: C, 62.7; H, 5.5; N, 6.4%); ν_{max} ($CHBr_3$) cm^{-1}; δ_H (200 MHz)

($CDCl_3$) 7.75-7.23 (10 H, m, aromatic protons), 6.91 (2 H, d, J = 7 Hz), 3.77 (3 H, s, N^+-$\underline{C}H_3$), 3.45 (3 H, s, N-$\underline{C}H_3$), 2.37 (3 H, s, -$\underline{C}H_3$), 2.21 (3 H, s, -$\underline{C}H_3$); δ_C (50 MHz) ($CDCl_3$) 170.0 (C-2), 144.2, 141.0, 140.6, 139.7, 138.3, 131.1, 128.5, 128.0, 125.9, 125.7, 125.6, 122.6, 122.5, 114.1 (other aromatic carbons), 47.4 (N^+-$\underline{C}H_3$), 37.1 (N-$\underline{C}H_3$), 21.1 (2 -$\underline{C}H_3$).

6.4.3 General Procedure for the Preparation of N-Methylated Amines (**6.6**)

The amidinium salt (**6.4**) or (**6.5**) (2 mmol) was dissolved in methylene chloride [4 ml for iodides (**6.4**) or 8 ml for p-methylbenzenesulfonates (**6.5**)]. Butylamine (2 mmol) was added with stirring and the solution was stirred at 25°C for 3 hours. The solvent was removed under reduced pressure (25°C/35 mmHg) and the residue dissolved in 1 ml of 95% ethanol. Potassium hydroxide pellets (1 g) were added to the solution to give a precipitate. The mixture was then stirred at 25°C for 3 hours. Water (4 ml) was added and the solution was extracted with diethyl ether (4 x 10 ml). The ether extracts were washed with water (5 ml), dried ($MgSO_4$), and the solvent was evaporated (25°C/35 mmHg) to give an oil that consisted of a mixture of the butyl imine (**6.7**) and the amine (**6.6**). The amine (**6.6**) was separated from (**6.7**) and purified as shown below. The boiling points and the ^1H NMR data of the amines (**6.6**) were in agreement with the values reported earlier.

3-Methyl-3*H*-benzothiazoline-2[N-(1-butyl)]imine (**6.7**)

Prepared in the average yield of 95%, as an oil, b.p. 99-106°C/1.5 mmHg (Found: C, 65.5; H, 7.3; N, 12.7. $C_{12}H_{16}N_2S$ requires: C, 65.4; H, 7.3; N, 12.7%); ν_{max} (neat) 1635s, 1590s cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 7.27 (1 H, d, J = 7 Hz), 7.11 (1 H, t, J = 8 Hz), 6.89 (1 H, t, J = 8 Hz), 6.75 (1 H, d, J = 8 Hz), 3.33 (3 H, s, -$\underline{C}H_3$), 3.17 (2 H, t, J = 7 Hz, -$\underline{C}H_2$-), 1.67 (2 H, quintet, J = 7 Hz, -$\underline{C}H_2$-), 1.43 (2 H, m, -$\underline{C}H_2$-), 0.95 (3 H, t, J = 7 Hz,

-$\underline{C}H_3$); δ_C (50 MHz) ($CDCl_3$) 155.2, 141.0, 125.9, 122.3, 121.7, 120.2, 107.9, 54.6 (-$\underline{C}H_2$-), 39.2 (-$\underline{C}H_3$), 29.8 (-$\underline{C}H_2$-), 20.4 (-$\underline{C}H_2$), 13.9 (-$\underline{C}H_3$).

N-Methyl-1-octylamine (**6.6.1**)

Prepared (88%) from (**6.4.1**) and separated from (**6.7**) by direct distillation from the reaction mixture, b.p. 125-135°C/90 mmHg {lit. b.p. 77.5-80°C/17 mmHg [52JA(74)1704]}; ν_{max} (neat) 3280m, 1375w cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 2.56 (2 H, t, J = 7 Hz, N-$\underline{C}H_2$), 2.50 (1 H, s, N$\underline{H}$), 2.40 (3 H, s, N-$\underline{C}H_3$), 1.51-1.40 (2 H, m, N-CH_2-$\underline{C}H_2$-), 1.40-1.10 (10 H, m, protons of the methylene groups), 0.90-0.80 (3 H, m, $C\underline{H}_3$); δ_C (50 MHz) ($CDCl_3$) 51.8, 36.0, 31.6, 29.5, 29.3, 29.0, 27.1, 22.4, 13.7.

N-Methyl-1-dodecylamine (**6.6.2**)

Prepared (85%) from (**6.4.2**) and separated from (**6.7**) by the modified procedure. Diethyl ether (10 ml) was added to the residue after the evaporation of CH_2Cl_2 and the precipitated amine hydroiodide was removed by filtration, treated with KOH and ethanol according to the general procedure. B.p. 110-120°C/1.5 mmHg (lit. b.p. 175-176°C [55MI153]); ν_{max} (neat) 3290m, 1375w cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 2.80 (1 H, broad peak, N$\underline{H}$), 2.60 (2 H, t, J = 7 Hz, N-$\underline{C}H_2$), 2.41 (3 H, s, N-$\underline{C}H_3$), 1.50-1.42 (2 H, m, N-CH_2-$\underline{C}H_2$-), 1.40-1.20 (18 H, m, protons of the methylene groups), 0.95-0.80 (3 H, m, $C\underline{H}_3$); δ_C (50 MHz) ($CDCl_3$) 52.1, 36.4, 31.9, 29.8, 29.6, 29.3, 27.3, 22.7, 14.1.

N-Methyl-1-cyclohexylamine (**6.6.3**)

Prepared (83%) from (**6.4.3**) and separated from (**6.7**) by direct distillation from the reaction mixture, b.p. 110-120°C/200 mmHg (lit. b.p. 61-63°C/35 mmHg [82MI3810]); ν_{max} (neat) 3250m, 1350s cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 3.41-3.40 (1 H, m, N$\underline{H}$), 2.41-2.36 (4 H, m, N-$\underline{C}$H, N$C\underline{H}_3$), 1.93-1.60 (5 H, m, protons of the cyclohexyl ring), 1.50-1.05 (5 H, m, protons of the cyclohexyl ring); δ_C (50 MHz) ($CDCl_3$) 57.9, 32.5, 32.2, 25.6, 24.5.

N-Methyl-1-phenylethylamine (**6.6.4**)

Prepared (85%) from (**6.5.1**) and separated from (**6.7**) by direct distillation from the reaction mixture, b.p. 110-115°C/35-40 mmHg (lit. b.p. 112-115°C/36-40 mmHg [82MI4624]); ν_{max} (neat) 3400s, 1370m cm^{-1}; δ_H ($CDCl_3$) 7.05 (5 H, m, aromatic protons), 2.7 (4 H, m, N-C<u>H</u>$_2$-C<u>H</u>$_2$-), 1.35 (1 H, s, N<u>H</u>); δ_C (25 MHz) ($CDCl_3$) 140.0, 128.6, 128.4, 126.0, 53.1, 36.2, 36.1.

N-Methylaniline (**6.6.5**)

Prepared (88%) from (**6.5.2**) and separated from (**6.7**) by column chromatography using CH_2Cl_2 as eluent. B.p. 80-90°C/15 mmHg (lit. b.p. 79.2°C/10 mmHg [82MI3731]); ν_{max} (neat) 3400s, 1400s cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 7.22-7.13 (2 H, m, H-3,5), 6.73-6.65 (1 H, m, H-4), 6.60-6.55 (2 H, m, H-2,6), 3.60 (1 H, broad, N<u>H</u>), 2.77 (3 H, s, N-C<u>H</u>$_3$); δ_C (50 MHz) ($CDCl_3$) 149.2, 129.1, 117.1, 112.3, 30.5.

N-Methyl-p-toluidine (**6.6.6**)

Prepared (84%) from (**6.5.3**) and separated from (**6.7**) by column chromatography, using CH_2Cl_2 as eluent. B.p. 92-95°C/8 mmHg (lit. b.p. 98-99°C/19 mmHg [82MI2068]); ν_{max} (neat) 3300s, 1470s cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 6.98 (2 H, d, J = 6 Hz, H-3,5), 6.52 (2 H, d, J = 6 Hz, H-2,6), 3.36 (1 H, s, N<u>H</u>), 2.76 (3 H, s, N-C<u>H</u>$_3$), 2.24 (3 H, s, C<u>H</u>$_3$); δ_C (50 MHz) ($CDCl_3$) 147.0, 129.6, 126.3, 112.5, 30.9, 20.3.

CHAPTER VII
SUMMARY

Application of benzotriazole as an auxiliary in synthetic transformations was investigated. The leaving ability of benzotriazole enabled development of new and unique synthetic methods for N-monoalkylation of primary amides and thioamides in a two-step sequence. The easy formation of benzotriazole amidoalkyl and amidoaryl derivatives thus allowed for the preparation of N-monoalkylated primary aliphatic and aromatic amides by reductive removal of the heterocyclic moiety with sodium borohydride. Using lithium aluminum hydride as a reducing agent, N-monoalkylated amines were obtained. The reaction of amidoalkyl and amidoaryl derivatives of benzotriazole with organomagnesium or organolithium reagents led to α-branched N-monoalkylated amides with formation of a new C-C bond. The developed synthetic method was shown to be of general utility, regioselective and proceeded in good overall yield.

An analogous method was applied to aromatic and heterocyclic thioamides and thioureas. The corresponding N-monoalkylated thioamides were obtained. This reaction could be carried out on a large scale using very common reagents. The reaction was applicable to aliphatic aldehydes only. Attempts to use aromatic aldehydes unexpectedly yielded 2,4,5-triphenyl-1*H*-imidazole as the sole product.

N-(Benzotriazol-1-ylmethyl) heterocycles were formed easily from 1-chloromethylbenzotriazole and the sodium salts of different NH-heterocycles. The benzotriazole moiety in these unsymmetrical aminals was stable to nucleophilic displacement by

hydride or organomagnesium compounds. N-(Benzotriazol-1-ylmethyl) heterocycles underwent smooth lithiation and subsequent reaction with a variety of electrophiles to give a new class of multifunctional compounds. The benzotriazole moiety provided activation of the methylene protons in such aminals and subsequent stabilization of the α-carbanions. Different sets of conditions were used in attempts to remove the benzotriazole moiety from aroyl and acyl derivatives of indole and carbazole. Only one case was successful. A Zn/HOAc mixture removed benzotriazole from (benzotriazol-1-yl)(indol-1-yl)-(benzoyl)methane. Application of the classical method for benzotriazole removal in this case was unsuccessful. Nucleophilic displacement on the carbon alpha to the carbonyl could be carried under basic conditions, by the classical S_N2 mechanism, or under acidic conditions, by the typical S_N1 mechanism. However, in this case both mechanisms would be disfavored because of the steric and electronic constraints.

The reactivity of 1-trimethylsilylbenzotriazole toward aliphatic and aromatic aldehydes and α,β-unsaturated ketones was studied. 1-Trimethylsilylbenzotriazole reacted easily with aliphatic and aromatic aldehydes to form adducts with the simultaneous transfer of the trimethylsilyl substituent from the heterocyclic nitrogen to the aldehydic oxygen. Attempts at lithiation of such compounds, however, were unsuccessful. Addition of 1-trimethylsilylbenzotriazole to α,β-unsaturated ketones proceeded in 1,4- fashion to give the corresponding silyl enol ethers with benzotriazole situated in the β-position. These products were very easily hydrolyzed to the corresponding ketones.

A method for the N-monomethylation of primary amines was also developed utilizing the benzothiazole moiety as a protecting group for the NH_2 functionality. 3-Methyl-2-thiomethylbenzothiazolium iodide reacted easily with primary aliphatic and aromatic amines to give the corresponding imine derivatives in good yields. Such compounds could be methylated on the imine nitrogen using readily available reagents.

Subsequent treatment with n-butylamine produced the final N-monomethylated amine product. This three-step sequence provides a general method for N-monomethylation of the primary aliphatic and aromatic amines.

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Throughout this work, references are designated by a number-letter coding of which the first two numbers denote tens and units of the year of publication, (or the the four digit number for the references published before 1900), the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time the reference is quoted. The system is based on that used in "Comprehensive Heterocyclic Chemistry", A. R. Katritzky and C. W. Rees Editors, Pergamon Press, New York (1985).

The following additional notes apply:

1. The list of references is arranged in order of (i) year, (ii) journal in alphabetical order of journal code (journal names are abbreviated according to CASSI [Chemical Abstracts Service Source Index] system), (iii) volume number or part number for journals that are published in parts, (iv) page number.

2. In the reference list the code is followed by the complete literature citation in the conventional manner.

3. Books and less common journals are given the code "MI" for miscellaneous.

4. Where journal have changed the names, the same code is used throughout, e.g. CB refers to both: Chem. Ber. and to Ber. Dtsch. Chem. Ges.

5. Patent literature is named using the code and additionally the chemical abstract reference is given.

Code	Journals
ACR	Acc. Chem. Res.
ACS	Acta Chem. Scan.
AG	Angew. Chem.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Org. Chem.
AP	Arch. Pharm. (Weinheim, Germany)
BCJ	Bull. Chem. Soc. Jpn.
BEP	Belg. Patent
BSF	Bull. Soc. Chim. Fr.
CA	Chem. Abstr.
CB	Chem. Ber.
CC	J. Chem. Soc. Chem. Commun.
CI(L)	Chem. Ind. (London)
CL	Chem. Lett.
CJC	Can. J. Chem.
CR	Chem. Rev.
CSR	Chem. Soc. Rev.
H	Heterocycles.
HCA	Helv. Chim. Acta.
IC	Inorg. Chem.
JA	J. Am. Chem. Soc.
JAP	Jap. Patent
JCR(S)	J. Chem. Res. (S).
JCS	J. Chem. Soc.

JCS(P1)	J. Chem. Soc. Perkin Trans. 1.
JCS(P2)	J. Chem. Soc. Perkin Trans. 2.
JGU	J. Gen. Chem. USSR (Engl.Transl.)
JHC	J. Heterocycl. Chem.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.
MIP	Miscellaneous Patent
LA	Liebigs Ann. Chem.
OMR	Org. Magn. Reson.
OR	Org. React.
PAC	Pure Appl. Chem.
RTC	Recl. Trav. Chim. Pays-Bas.
SA	Spectrochim. Acta
SC	Synth. Commun.
S	Synthesis
T	Tetrahedron
TL	Tetrahedron Lett.
UP	Unpublished work
USP	U.S. Patent

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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